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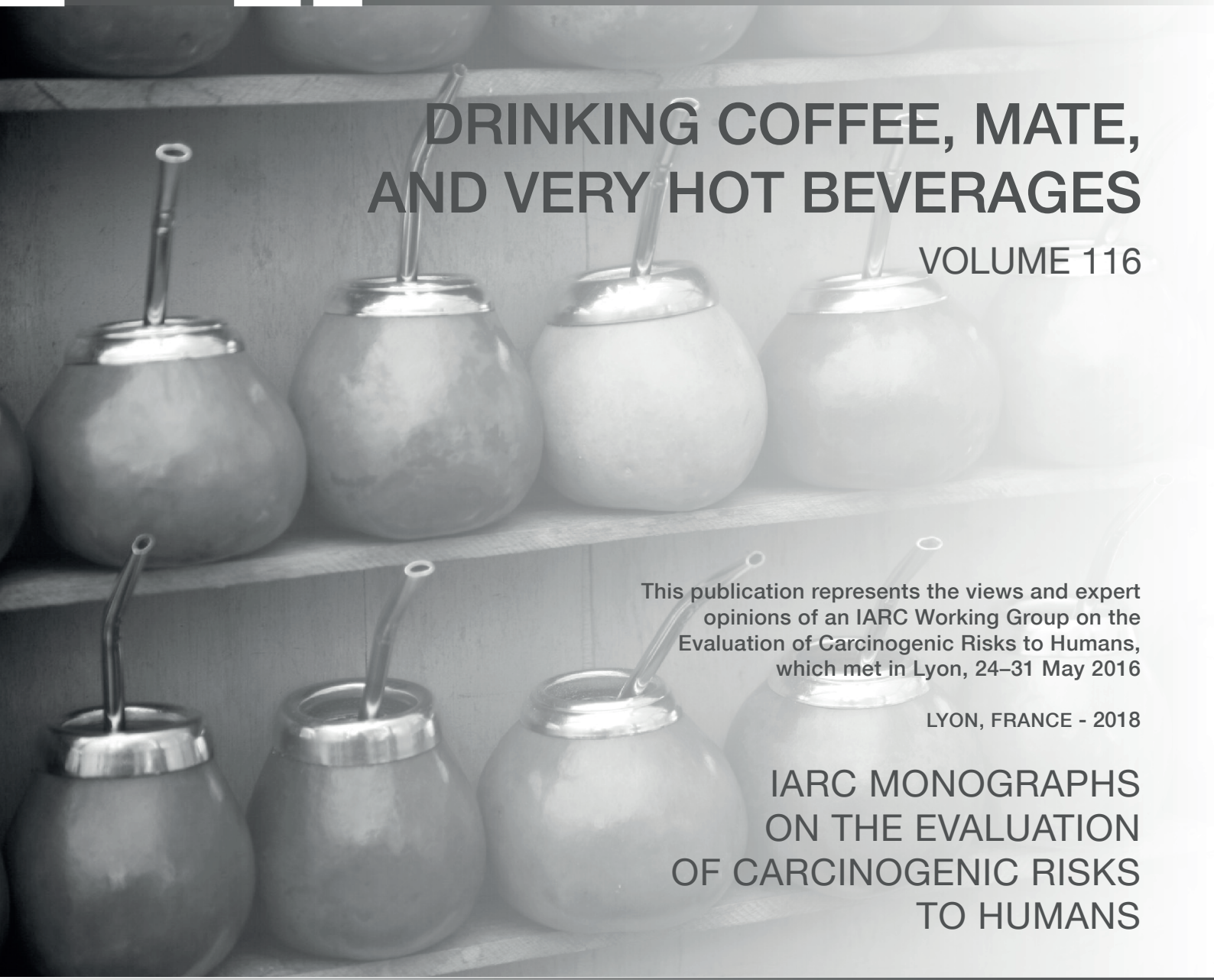

DRINKING COFFEE, MATE, AND VERY HOT BEVERAGES

VOLUME 116

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DRINKING MATE AND VERY HOT BEVERAGES

1. Exposure Data

Beverages, or drinks, are liquids intended for human consumption. Hundreds of different drinks are consumed by humans to replenish water loss or to receive nutrients and energy, as well as for social and cultural purposes. The major component of all drinks is water.

There is no universally accepted definition of hot or very hot beverages, and the standards may vary according to the type of beverage and geographical location. High temperatures, in addition to helping dissolve chemical constituents and flavour compounds, partly inactivate pathogenic microorganisms and toxins, warm the body, and optimize the taste and sense of satisfaction provided by certain beverages. Tea and coffee are the most common hot drinks consumed worldwide but there is a long list of others, including alcoholic and non-alcoholic drinks. Notable examples include mate, hot chocolate, diverse herbal infusions, hot mulled wine or cider, hot calvados (an apple liqueur produced in France), and hot sake (a Japanese alcoholic drink made from rice). Other hot liquids consumed by humans include bouillon, other hot broths, and hot soups.

The carcinogenicity of mate was reviewed in Volume 51 (IARC, 1991). Since that time, pertinent new data for mate and other hot beverages have become available and are reviewed in this volume.

1.1 Identification of the agent

1.1.1 Very hot beverages

Hot beverages are typically served between 71 °C and 85 °C (Brown & Diller, 2008). In general, they are consumed at temperatures lower than the initial serving temperature, typically between 50 °C and 70 °C. However, the consumers' choice of the drinking temperature may vary to a wide degree. A study taking into account consumer preference and scalding hazards suggested that the optimal temperature for drinking coffee is approximately 58 °C (Brown & Diller, 2008). [Sensory acceptance may be negatively influenced at temperatures below 60 °C (see Section 4).]

Standard methods for preparing test samples of hot beverages specify different temperatures according to the beverage. The International Organization for Standardization (ISO) standard for preparation of a liquor of tea for use in sensory tests specifies that boiling water should be used for preparation, and that the temperature should be in the range of 65–80 °C when milk is added (ISO, 1980). The ISO standard for the preparation of coffee samples for use in sensory analysis specifies that the beverage must be allowed to cool to a temperature of 55 °C or below, and that the first tasting is usually at a temperature between 50 °C and 55 °C (ISO, 2008).

There is a wide variation in temperature preferences across geographical regions. The Royal Society for Chemistry in the United Kingdom has

suggested drinking tea at temperatures between 60 °C and 65 °C (Royal Society of Chemistry, 2003). A study of 300 patients with indigestion in the UK (Edwards & Edwards, 1956) found that their mean preferred tea drinking temperature was between 53 °C and 57 °C. Ghadirian (1987) compared preferred drinking temperatures for black tea between areas of the Islamic Republic of Iran with low and high incidence of cancer of the oesophagus. In the region with low incidence, 72% of subjects drank their tea at temperatures below 55 °C, whereas in the region with high incidence, 62% drank tea at temperatures over 65 °C. Another study in an area of the Islamic Republic of Iran with a high incidence of cancer of the oesophagus showed that 56% of healthy subjects drank their tea at temperatures between 60 °C and 69 °C, while 39% drank tea below 60 °C and 5% at 70 °C or higher (Islami et al., 2009a). Finally, when studying 188 people in the Kilimanjaro region of the United Republic of Tanzania, Munishi et al. (2015) found that the mean temperature of tea at the first sip was approximately 71 °C.

In a study in the USA (Lee & O'Mahony, 2002), 300 consumers were asked to mix a hot coffee with cooler coffee until the desired temperature for drinking was reached. The chosen mean preferred drinking temperature was 60 °C with a range of 37–88 °C.

A study in Pelotos, Brazil, showed that the median drinking temperature for mate was 69.5 °C (Victora et al., 1990). Men drank mate at significantly higher temperatures than women (71.1 °C vs 67.6 °C, $P < 0.001$).

[The Working Group noted that the variation in mean drinking temperature in these studies was quite substantial. This may be partly due to variations in participant populations (e.g. in the study of Edwards & Edwards (1956) on patients with indigestion) or measurement methods (e.g. measuring when the first sip is taken vs another time point). However, differences in taste preferences in different geographical regions most likely account for most variation. In view of the few representative studies that were available, the Working Group considered that beverages drunk at temperatures in the range of 50–65 °C be classified as "hot beverages" and beverages above 65 °C as "very hot beverages".]

1.1.2 Mate

(a) Introduction

The term "mate" is used ambiguously in the literature for the infusion, that is, the consumed beverage (sometimes referred to as mate tea or yerba mate), the dried leaves from which it is made, and the plant that produces the leaves. Where unambiguous terminology is needed in this monograph mate will refer to the consumed beverage, while the other materials will be specified as "mate tree" or "mate leaves", for example. The term "mate de coca", which is sometimes used to define an infusion of coca leaves, is a misnomer and should be avoided.

The mate plant is native to the area of South America between latitudes 18° S and 35° S, from the Atlantic Ocean to the Paraguay River. This area includes northern Argentina, the south of Brazil, Paraguay, and Uruguay. Mate was originally consumed by indigenous populations of Argentina, Paraguay, and regions near Brazil and Uruguay before the Spanish arrived in the 16th century (IARC, 1991; Bracesco et al., 2011). Jesuit priests began cultivation of selected varieties of the mate tree in the 17th century and introduced the practice of drinking mate as a hot beverage (Graham, 1984; IARC, 1991; EMA, 2010).

(b) Botanical data and nomenclature

Botanical name: *Ilex paraguariensis* A. St.-Hil
Family: Aquifoliaceae
Genus: *Ilex*
Common names: erva mate, yerba mate, maté, Jesuits' tea, Brazilian tea, Paraguay tea (GRIN 2016)

Fig. 1.1 *Ilex paraguariensis* A. St.-Hil

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(c) Description

Mate is prepared from the leaves of *Ilex paraguariensis*, a subtropical dioecious evergreen tree. The mate tree is a flower- and fruit-producing plant. The tree is usually cultivated as a shrub 3–6 m tall with numerous stems. The leaves are dark green, 15–20 cm in length, and short-stalked with an acuminate tip and finely dentated edges. It has small white flowers, which grow in forked clusters in the axils of the leaves, and violet-black berries, each of which contains four to eight seeds (Graham, 1984; Vázquez & Moyna, 1986; IARC, 1991; Fig. 1.1).

1.2 Production and use

The production and use of mate are reviewed in this monograph. Parallel information for coffee is provided in the monograph on Coffee Drinking in the present volume.

1.2.1 Mate

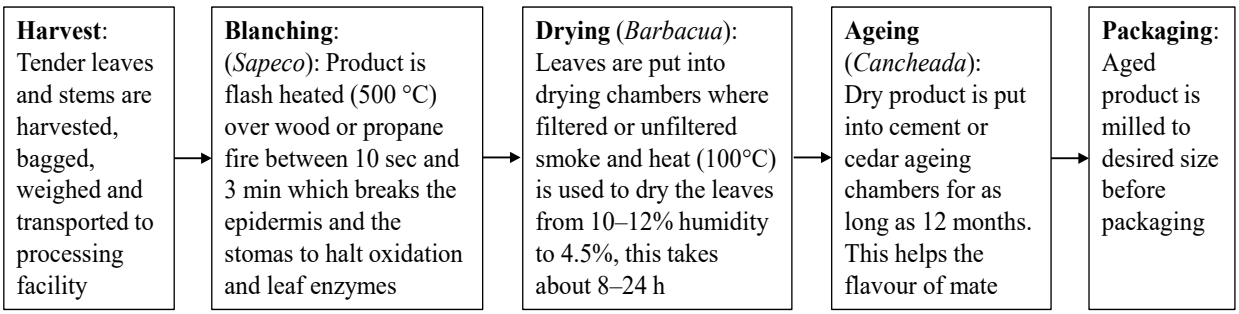
(a) Production

The cultivation and harvesting of mate is conducted by various methods depending on the region. The three primary methods of cultivation and harvest are: (1) extractive exploitation of the natural forest, (2) mixed system, and (3) cultivated plantations (Giberti, 1994).

Mate leaves are harvested when the trees are 4–6 years old. Leaves and small stems are harvested, either manually or mechanically, weighed, bagged, and transported to a processing facility (Heck & de Mejia, 2007).

The leaves are processed before reaching the consumer. Fresh mate leaves may undergo several of the following stages: blanching/flash-heating, roasting, drying, ageing, milling, and packaging. The conditions for each of these stages vary widely depending on the country or region, producer, and the final objective for the desired style and flavour of the finished drink. The overall process

Fig. 1.2 Processing of *Ilex paraguariensis* leaves into mate tea products



Created using data from Schmalko & Alzamora (2001)

is generally the same, however (Fig. 1.2; Heck & de Mejia, 2007).

Post-harvesting steps and their important effects on the chemical properties of mate are described below.

(i) Flash-heating

Flash-heating, which is a dry process, is sometimes called "blanching" or "scorching". This phase of the process consists of rapidly heating the mate leaves with the objective of inactivating enzymes (i.e. polyphenol oxidase), slowing down the natural decomposition of the plant material, and preserving sensory qualities. Traditionally, this process was performed by direct exposure to an open wood fire or propane in a rotating oven. At present, most old stoves have been replaced by automatic conveyor-belt dehumidifiers blowing hot air into the leaves (Peralta & Schmalko, 2007; Zaions et al., 2014). During industrial flash-heating with hot gases at temperatures above 500 °C, the leaves lose about 70% of their water content (Schmalko & Alzamora, 2001).

(ii) Drying

Traditionally, two systems are used to dry the leaves: *carijo* (scorched) and *barbacua* (smoke or hot air) (Fig. 1.3). When using the *carijo* method, the heat of the fire goes directly to the leaves. If the *barbacua* process is employed, the hot air (about 100 °C) or filtered or unfiltered smoke reaches the leaves indirectly through a tunnel under the earth.

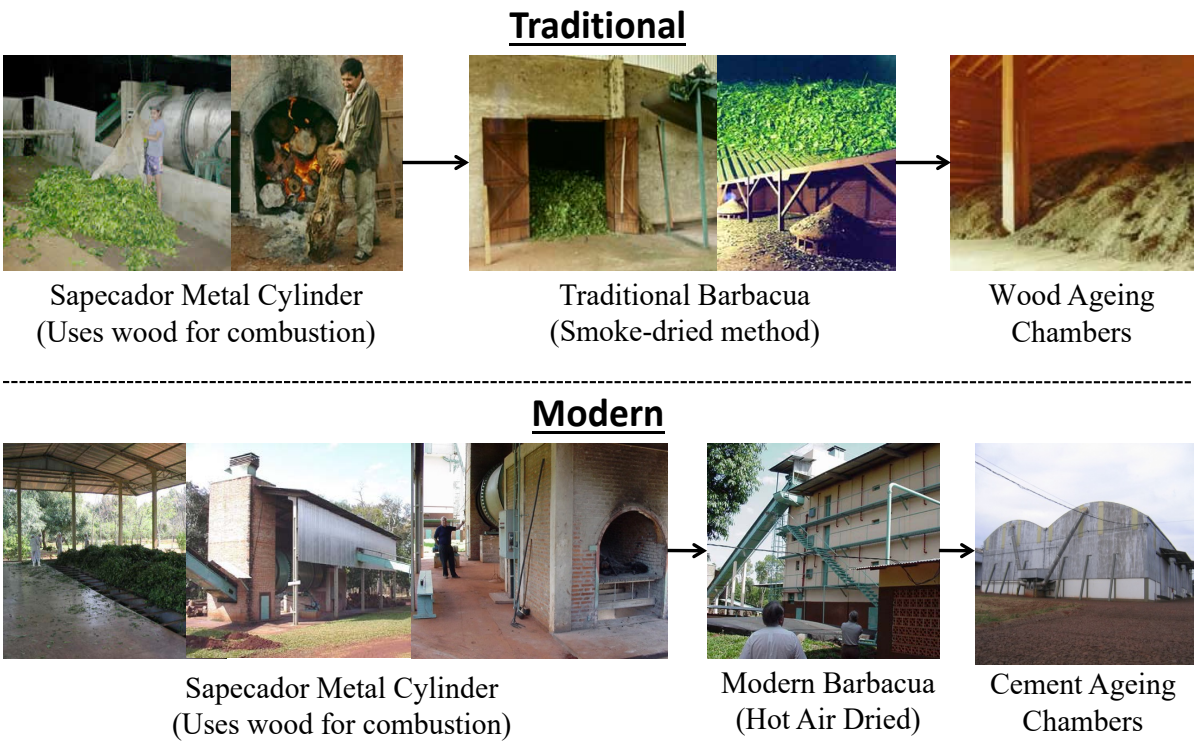
(iii) Ageing

Dried leaves may also be aged to develop specific colours and flavours, especially popular in Chile and Uruguay (Zaions et al., 2014). In the traditional ageing process, dried leaves that have been cut into smaller pieces are left in ageing chambers for a minimum of six months and up to one year or more. Ageing significantly increases the concentration of some of the components, such as methylxanthines and total phenolics (see Section 1.4), as well as the antioxidant activity of mate extracts (Blum-Silva et al., 2015). Improved methods for preserving the characteristics of the mate during storage have recently been developed (e.g. Prestes et al., 2014). The ageing step may be omitted for consumption in Brazil, where green leaves are preferred (Zaions et al., 2014).

(b) Use

The consumption of mate has expanded to millions of consumers in South America, but also to some countries in North America, Europe, and the Middle East. In South America, mate is drunk in social settings and can have important ritualistic connotations (Bracesco et al., 2011).

Fig. 1.3 Drying of mate leaves



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Mate has also been used in traditional herbal medicinal products for centuries in South America and for several decades in European countries and the USA (EMA, 2010). More recently, mate leaves or extracts have been used as an ingredient in so-called energy drinks and in dietary supplements in the USA and Europe (Heck & de Mejia, 2007; Bracesco et al., 2011; Winkler et al., 2014).

(i) Hot mate

The method of preparing the mate infusion varies considerably from one region to another. In Argentina, southern Brazil, Chile, Paraguay, and Uruguay, mate is traditionally prepared for consumption by placing the dried and ground mate leaves into a hollow calabash gourd known commonly as a mate, *cuia*, or *guampa* (Fig. 1.4). Hot water [70–80 °C (158–176 °F)] is added and the resulting infusion is drawn by mouth with a metal straw called a *bombilla*. The *bombilla* acts as both a straw and a sieve. The submerged end is flared, with small holes or slots that allow the brewed liquid to be sipped while preventing aspiration of solid material (Bracesco et al., 2011). The gourd may be refilled with hot water many times before the mate leaves become washed out and lose their flavour. Consumption of around 1–2 L of brewed mate per day is common (Bracesco et al., 2011).

In addition to the traditional mate preparation, "teabag"-type infusions of mate are common, particularly in importing countries (e.g. Asia, Europe, and the USA).

Fig. 1.4 Mate in a traditional calabash gourd

(ii) Cold mate

Mate drinks made from toasted or green mate leaves can be prepared from loose or bagged leaves, with added sugar, and consumed cold. Ready-to-drink commercial mate products for cold consumption are also available.

(iii) Other mate products

Mate has traditionally been used as a medicinal product for symptoms of fatigue or a sensation of weakness, as a diuretic, and for minor urinary complaints (EMA, 2010).

New mate products have recently been developed due to the availability of mate powder extract. Mate extracts are an ingredient in various foods (sport liquid gel/chew and sweets) and energy drinks as a source of caffeine (Heckman et al., 2010a, b). A survey of the German market in 2014 detected 26 mate-containing products, predominantly alcohol-free soft drinks and energy drinks (Winkler et al., 2014).

Mate products are also marketed in Europe and North America as dietary supplements in tablet form. For example, the US Dietary Supplements Label Database lists more than 70 products that contain *Ilex paraguariensis* on the label (NLM, 2016).

(c) Chemical composition

(i) Major constituents

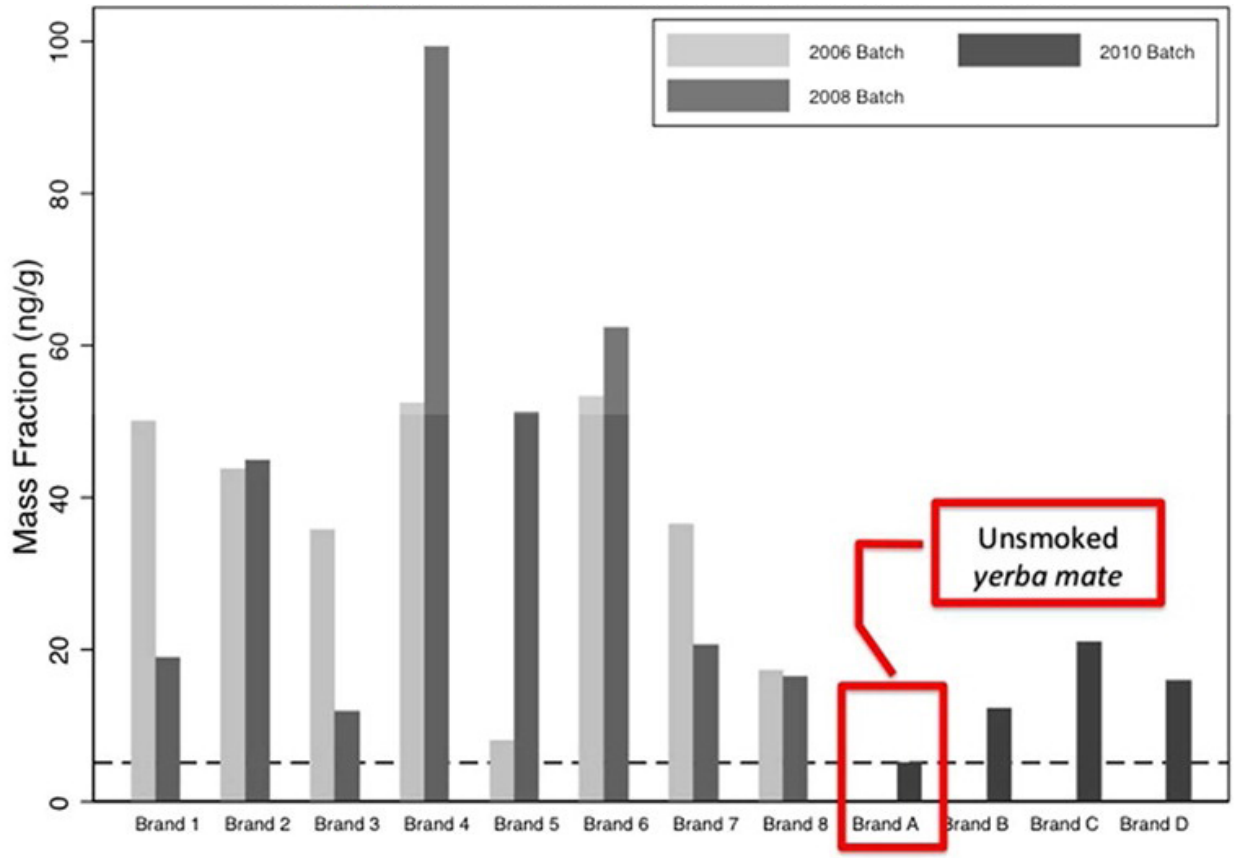
Similar to coffee (see monograph on Coffee Drinking in this volume) and *Camellia sinensis* tea (see IARC, 1991), caffeine is one of the principal components in mate with pharmacological effects; the mild stimulating effect of this beverage may be the reason for its popularity (Lachenmeier et al., 2012).

Depending on preparation, the chemical composition of the mate beverage may vary largely: the caffeine concentration in the final beverage is 270–540 mg/L (Heckman et al., 2010b).

Very few studies have reported on chlorogenic acid contents in mate. Marques & Farah (2009) reported concentrations in the order of 0.5 g/L of total chlorogenic acids in green mate and 0.1 g/L in toasted mate. In contrast, total polyphenol content in 13 traditional products were reported to range from 3.4 g to 7.4 g of chlorogenic acid equivalent (CH) per litre of freshly prepared mate, and from 0.02 g to 1.80 g of CH/L in 11 non-traditional mate beverages (Gonzalez de Mejia et al., 2005). [The Working Group concluded that the difference is likely related to the presence of additional ingredients such as sugars, fruit pieces, amino acids, vitamins, and flavouring agents in non-traditional mate beverages.]

[The Working Group noted that no systematic or representative data are available on mate composition, and the limited knowledge is based on single-sample studies. In addition, available studies vary largely in the method of preparation of the beverage for analysis in terms of origin of the leaves used, amount of leaves per litre of water, temperature, brewing time, and filtration. Further, not all studies report information in enough detail for comparison.]

Fig. 1.5 Benzo[*a*]pyrene concentration in processed mate leaves sampled in 2006, 2008, and 2010



The dashed line shows the benzo[*a*]pyrene content of the mate brand that never touched smoke (Brand A, marked with square). Adapted with permission from Golozar et al. (2012). Significant variation in the concentration of carcinogenic polycyclic aromatic hydrocarbons in yerba maté samples by brand, batch, and processing method. *Environmental Science & Technology*. Copyright (2012) American Chemical Society

(ii) Potential contaminants

Depending on the processing method (especially the drying steps), the content of polycyclic aromatic hydrocarbons (PAH) in mate leaf material sampled at fresh, partially dried, and dried stages of production may vary to a large degree (0.4–9 mg/kg total PAHs) (Vieira et al., 2010). Another study reported median total PAH contents of 0.6–3.7 mg/kg in samples of commercial mate leaf brands in 2008 and 2010; the significant variation observed was dependent on batch and processing method, including whether products were produced with or without exposure to smoke (Golozar et al., 2012). The content of benzo[*a*]pyrene, most probably from exposure to smoke during the mate manufacturing, ranged over 11.9–99.3 µg/kg of product. The samples processed without exposure to smoke had the lowest benzo[*a*]pyrene content (Fig. 1.5; Golozar et al., 2012).

Kamangar et al. (2008) reported that approximately 37% of the total PAH content (21 PAH analysed) found in the leaves of commercial mate material from Brazil [no details about samples provided] may be transferred into the mate infusion (Kamangar et al., 2008). A total PAH content of 0.6–2.3 µg/L was detected in prepared mate from Brazil [no details about samples provided],

Table 1.1 Compounds that may be present in mate and that have been evaluated previously by IARC

Agent	Concentration in mate	*IARC Monographs* evaluation of carcinogenicity			*IARC Monographs* Volume (year)
		In animals	In humans	IARC Group	
Caffeine	0.5–2% in the leaves	Inadequate	Inadequate	3	51 (1991)
Theobromine	Less than 1% in the leaves	No data	Inadequate	3	51 (1991)
Benzo[*a*]pyrene	Traces	Sufficient	No data	1	100F (2012)
Naphthalene	Traces	Sufficient	Inadequate	2B	82 (2002)
Acenaphthene	Traces	Inadequate	No data	3	92 (2010)
Phenanthrene	Traces	Inadequate	No data	3	92 (2010)
Caffeic acid	Traces	Sufficient	No data	2B	56 (1993)

No systematic data were available on concentrations of these agents in mate tea; mate also contains traces of several additional polycyclic aromatic hydrocarbons evaluated in *IARC Monographs* Volume 92 in 2010 into Groups 2A, 2B, and 3

with naphthalene, acenaphthene, and phenanthrene having the highest concentrations (Zuin et al., 2005).

Based on analyses of the PAH metabolite 1-hydroxypyrene glucuronide (1-OHPG) in 199 healthy adults, mate drinking was statistically significantly associated with higher urine concentrations of 1-OHPG (Fagundes et al., 2006).

Of the compounds evaluated in the *IARC Monographs* that have been described to occur in mate (Table 1.1), benzo[*a*]pyrene was evaluated as *carcinogenic to humans* (Group 1).

[The Working Group noted that the data available on PAH occurrence in mate leaves and mate infusion were based on small studies with non-representative sampling. No systematic monitoring data on PAH exposure related to mate consumption were available to the Working Group. Information on other potentially production-related contaminants such as acrylamide or furan was also unavailable.]

1.3 Production and consumption data

The major worldwide producers of mate leaves are Brazil (primarily southern Brazil), Argentina, and Paraguay. The total world production of processed mate leaves for 2012 was 821 534 tonnes, comprising 513 256 tonnes (62%) from Brazil, 250 928 tonnes (31%) from Argentina and 57 350 tonnes (7%) from Paraguay (FAO, 2016). Fig. 1.6 highlights the regions of South America where mate is produced commercially (Heck & de Mejia, 2007). Table 1.2 provides data describing the trends in production of mate leaves during 2002–2012.

Table 1.3 lists the average volume of production, exports, and imports of mate leaves during 2010–2013 in the main mate-producing countries. Brazil and Argentina have largely increased their production in recent years. The main destination countries for exports were Uruguay, Syrian Arab Republic, Chile, and Brazil (FAO, 2016).

Data on per capita consumption of mate beverages were not systematically available to the Working Group.

1.4 Methods of measurement and exposure assessment

1.4.1 Beverage temperature

Over the past few decades, many epidemiological studies have investigated the association between the consumption of hot drinks and

Fig. 1.6 Map of South America showing growing regions for *Ilex paraguariensis*

1 Argentina; 2 Brazil, 3 Paraguay, 4 Uruguay
Adapted from Heck & de Mejia (2007). Yerba mate tea (Ilex paraguariensis): a comprehensive review on chemistry, health implications, and technological considerations. *Journal of Food Science*, 72: R138–R151

cancer. Exposure to hot drinks has been assessed using various methods, including: asking direct questions of participants, administering structured questionnaires, and measurement of the drinking temperature of consumed beverages.

While it would be desirable to directly measure the temperature at which drinks are consumed, studies have instead typically relied on questionnaires to assess the participants' preference for drinking temperature as well as the type, duration, and frequency of drinking (Islami et al., 2009b). For example, participants may be asked to describe their usual temperature preference by subjective categories such as "cold", "warm", "hot", or "very hot".

Data on the volume consumed per day or drinking frequency, total duration of drinking, sip volume, and drinking temperature could also be valuable. However, in a systematic review of hot drinks in relation to cancer of the oesophagus based on 59 published studies, Islami et al. (2009b) concluded that many of the studies did not collect data on several of these factors or did not report the results, as investigating the effects of hot drinks was not the main aim of most studies. Furthermore, few studies adjusted the results of drinking temperature for the amount consumed and vice versa. The potential for interviewer or recall bias is also a concern, given the subjective nature of questions about temperature

Table 1.2 Trends in production of mate, 2002–2012

Country	Production (× 1000 tonnes)										
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Brazil	513.5	501.7	403.3	429.7	434.5	438.5	434.7	443.1	602.6	443.6	513.3
Argentina	285.0	285.0	251.9	265.1	280.0	290.0	237.9	228.5	250.7	245.4	250.9
Paraguay	136.6	89.0	76.7	74.0	86.1	87.5	76.7	76.7	85.5	85.5	57.3

Official data from the Food and Agriculture Organization of the United Nations (FAO, 2016)

Table 1.3 Production, exports, and imports of mate for the main producing countries and selected importing countries (average for 2010–2013)

Country	Production[a] (tonnes)	Exports[b] (tonnes)	Imports[c] (tonnes)
Brazil	518 725	35 716	2 899
Argentina	247 518	36 110	184
Paraguay	78 541	666	87
Uruguay	—	203	31 691
Syrian Arab Republic	—	81	23 495
Chile	—	—	6 599
Germany	—	474	977
Lebanon	—	—	1 144
France	—	380	582

[a] Official data from the Food and Agriculture Orgnization of the United Nations (FAO, 2016)
[b] From Vasconcelos de Oliveir & Dabdab Waquil (2015)
[c] Only three states in Brazil have mate drinkers in their population (lowering the per capita intake), but up to 70% of the male population in the states of Rio Grande do Sul, Santa Catarina, and Parana drink mate daily (Bracesco et al., 2011)

and the retrospective case–control design of most studies.

Very few epidemiological studies have assessed the reliability of reported temperature by using two or more measures. In a case–control study of cancer of the oesophagus and drinking hot tea, Islami et al. (2009a) used two independent questions regarding preference for tea temperature (lukewarm or warm, hot, and very hot) and time from pouring tea to drinking it (≥ 4, 2–3, and < 2 minutes). These two measures were strongly correlated (weighted kappa = 0.68), and both were strongly associated with a higher risk of cancer of the oesophagus.

In the pilot phase of a cohort study in Golestan Province of the Islamic Republic of Iran (Pourshams et al., 2010), the investigators tested two methods to measure the drinking temperature of tea; one of these showed good reliability (weighted kappa = 0.71) and was used for the actual cohort study. In brief, the investigators prepared a fresh cup of tea for each participant and measured the temperature of the tea using a digital thermometer. When the temperature was 75 °C, they asked the participants to sip the tea and say whether that was the temperature at which they usually drank tea. If not, the tea was allowed to cool by increments of 5 °C and the question was repeated until the temperature at which tea was usually drunk was reached (Islami et al., 2009a).

Islami et al. (2009a) studied the reliability of this method in the 48 524 cohort participants, and found that self-report of the drinking

temperature of tea (lukewarm or warm, hot, very hot) was positively correlated with the actual measured temperature (kappa = 0.49; $P = 0.005$) and inversely correlated with the time from pouring tea to drinking it (kappa = 0.68; $P = 0.03$).

Further methods of assessing the temperature of hot beverages were investigated in a cross-sectional study in the north of the United Republic of Tanzania, an area of high risk of cancer of the oesophagus (Munishi et al., 2015). Drinking temperatures of tea were measured using methods similar to those of the Golestan cohort study in the Islamic Republic of Iran. Participants were asked to prepare, pour, and drink tea in the normal manner. Temperatures were measured in an identical cup of tea poured at the same time. Participants started drinking the tea at a mean temperature of 70.6 °C (standard deviation, 3.9), and the temperature of the last of the tea before the full cup was consumed was 60.2 °C (standard deviation, 4.0). The two main types of tea consumed in the area were milky tea (milk and water boiled together in tea preparation) and black tea (no milk). Milky tea drinkers drank their tea 1.9 °C (95% CI, 0.9–2.9) hotter than drinkers of black tea, as black tea cooled twice as fast as milky tea. The temperature of the tea at which men started drinking was 0.9 °C (95% CI, −0.2 to 2.1) higher than that for women, and men finished their cups faster. Most participants self-reported their tea drinking as hot, but the measurements showed that over 90% of participants began drinking when the temperature of the tea was > 65 °C. A new exposure assessment tool additionally examined in this study was self-reported history of tongue/mouth burning from hot beverages. A strong positive correlation was found between a positive history and measured temperature of the beverage being consumed.

2. Cancer in Humans

2.1 Mate

See Table 2.1 and Table 2.1.2 (web only; available at: http://publications.iarc.fr/566).

A previous Working Group reviewed and evaluated the potential carcinogenicity of mate in Volume 51 (IARC, 1991). At that time, the available data included only seven relatively small case–control studies, three of which reported results on cancer of the oesophagus. In that evaluation, mate overall was considered *not classifiable as to its carcinogenicity to humans* (Group 3), while the Working Group concluded that there was *limited evidence* from studies in humans for the carcinogenicity of hot mate. Hot mate drinking was evaluated as *probably carcinogenic to humans* (Group 2A).

Since the previous evaluation, many more studies in humans have been published. All these studies have been conducted in South America, primarily in Uruguay but also in Argentina, Brazil, and Paraguay. The large majority of these studies have hospital-based case–control designs, with cases and controls coming from the same hospital, and are frequency- or individual-matched for age, sex, place of residence, and other covariates. Controls were selected from patients whose diseases were presumed to be unrelated to the case risk factors. Nearly all studies had very high (> 90%) case and control participation rates.

Some of these studies (mostly the more recent) focused on mate, while others (mostly older studies) investigated mate as part of a case–control study of several risk factors. Studies that focused on mate tend to have more extensive questions on the duration of mate drinking, typical frequency of drinking, daily quantity of consumption, and drinking temperature. More recent studies (typically those published after 1995) were more likely to use regression models to adjust for confounders and were therefore able

Table 2.1 Case–control studies on cancer of the oesophagus and drinking mate

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Cancer	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Castellsagué et al. (2000) Argentina, Brazil, Paraguay, Uruguay 1986–1992	Cases: 830 from hospitals and clinics in each study area (La Plata, Argentina; Porto Alegre and Pelotas, Brazil; Asuncion, Paraguay; Montevideo, Uruguay); histologically confirmed Controls: 1779 patients admitted to the same hospital during the same period, and matched for sex and age Exposure assessment method: questionnaire	Oesophagus (SCC)	Mate drinking status: Ever Former Current Mate amount (L/day): 0.01–0.5.0 0.51–1.00 1.01–1.50 1.51–2.00 > 2.00 Trend test *P* value, 0.0001 Mate temperature: Cold/ warm Hot Very hot Trend test *P* value, 0.008	 770 115 655 232 283 88 96 68 127 536 99 	 1.52 (1.10–2.12) 1.87 (1.25–2.80) 1.47 (1.06–2.05) 1.39 (0.98–1.98) 1.34 (0.95–1.90) 1.96 (1.27–3.03) 2.03 (1.32–3.13) 3.04 (1.84–5.02) 1.00 1.11 (0.84–1.47) 1.89 (1.24–2.86) 	Age, hospital, residence, education, cigarette smoking, alcohol intake, sex	IARC multinational study Strengths: pooled analysis of several studies with a large sample size, examining the interaction between mate amount and temperature Limitations: the question on mate temperature was about subjective perception of temperature
Szymańska et al. (2010) Seven centres in South America (Buenos Aires in Argentina; Goiania, Pelotas, Porto Alegre, Rio de Janeiro, and Sao Paolo in Brazil; and La Havana in Cuba) 1998	Cases: 80 patients with UADT cancers (including oesophageal) newly diagnosed or referred with no prior treatment in participating hospitals Controls: 240 in- or out-patients at the same hospitals as the cases Exposure assessment method: questionnaire	Oesophagus	Mate drinking status: Ever Mate temperature: Never drinker Cold/ warm Hot/very hot Trend test *P* value, 0.012	 157 9 15 56 	 3.81 (1.75–8.30) 1.00 7.52 (2.72–20.82) 3.33 (1.51–7.35) 	Age, sex, centre, education, tobacco smoking, alcohol drinking Age, sex, centre, education, tobacco pack-years, and alcohol gram-years	Limitations: the question on temperature was about subjective perception

Table 2.1 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Cancer	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sewram et al. (2003) Uruguay 1988–2000	Cases: 344 hospital-based, ascertained from the medical records of the Oncology Institute of Montevideo Controls: 469 hospital-based, from the same institute as cases Exposure assessment method: questionnaire	Oesophagus (SCC)	Mate drinking status			Age, sex, urban vs rural residence, education, smoking, alcohol intake	Limitations: the question on temperature was about subjective perception
			Ever	327	2.26 (1.19–4.27)		
			Mate temperature			As above	
			Non-drinkers	15	1.00		
			Warm/ hot	241	2.00 (1.05–3.81)		
			Very hot	54	3.98 (1.98–8.44)		
			Trend test *P* value, 0.004				
			Amount of mate consumption (L/day)			As above plus temperature and duration of consumption	
			0.01–0.50	73	1.69 (0.85–3.35)		
			0.51–1.00	152	2.47 (1.28–4.77)		
			≥ 1.01	102	2.84 (1.41–5.73)		
			Trend test *P* value, 0.02				
			Mate temperature among mate drinkers			As above plus amount and duration of mate consumption	
			Warm/ hot	241	1.00		
			Very hot	54	1.87 (1.17–3.00)		
			Mate consumption among mate drinkers (L/day):			Age, sex, urban vs rural residence, education, smoking, alcohol intake, temperature and duration of mate consumption	
			0.50–1.01	152	1.49 (1.00–2.23)		
			≥ 1.01	102	1.62 (1.01–2.62)		
			Trend test *P* value, 0.3				

Table 2.1 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Cancer	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lubin et al. (2014) Argentina, Brazil, Paraguay and Uruguay 1986–2005	Cases: 1400 hospital-based cases for IARC multinational study; in Uruguay, cases were ascertained from records of the Oncology Institute of Montevideo Controls: 3229 hospital-based; in Uruguay, patients with conditions unrelated to tobacco smoking and alcohol drinking, without recent changes in diet Exposure assessment method: questionnaire	Oesophagus (SCC)	Mate temperature			Study, age, sex, education, smoking (pack-years, cigarettes/day), alcohol consumption (drink-years, drinks/day) and for Uruguay income and urban vs rural residence Study, age, sex, education, cigarette smoking (pack-years, cigarettes/day), alcohol consumption (drink-years, mL ethanol/day) and for Uruguay income and urban vs rural residence	Pooled analysis of the IARC multinational study and another study from Uruguay (Castellsagué et al., 2000) Strengths: pooled analysis of several studies with a large sample size; examining the interaction between mate amount and temperature Limitations: the question on temperature was about subjective perception
			Never drinker	83	1.0		
			Warm	168	1.2 (0.8–1.7)		
			Hot	929	1.6 (1.2–2.2)		
			Very hot	213	2.2 (1.5–3.1)		
			Trend test *P* value, 0.01				
			Excess OR (L/day–yr) stratified by mate temperature				
			Warm	NR	0.004 (0.002–0.013)		
			Hot	NR	0.007 (0.003–0.013)		
			Very hot	NR	0.016 (0.009–0.027)		
			Trend test *P* value, < 0.01				
Dietz et al. (1998) Rio Grande do Sul, Brazil 1990–1991	Cases: 55 from the Endoscopy Service of General Hospital, Porto Alegre Controls: 110 patients undergoing endoscopy for gastroenterological complaints, with no evidence of cancer on the endoscopy Exposure assessment method: questionnaire	Oesophagus	Mate temperature			NR	Limitations: the question on tea temperature was about subjective perception of temperature
			Not hot	NR	1.00		
			Hot or very hot	39	2.55 (1.01–6.56)		

Table 2.1 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Cancer	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vassallo et al. (1985) Montevideo, Uruguay 1979–1984	Cases: 226 incident oesophageal SCC identified from the Cancer Registry at the Oncology Institute of Montevideo; histologically confirmed Controls: 469 other cancer cases from the same registry (common diagnoses were cancer of the skin, colorectum, prostate, and breast) Exposure assessment method: questionnaire; questionnaire administered at the time of admission to all patients	Oesophagus (SCC)	Mate consumption (men, L/day)			Age and tobacco and alcohol use	Limitations: controls were cancer patients
			Non-users	10	1.0		
			0.01–0.49	12	1.1 (0.2–5.0)		
			0.50–0.99	82	3.1 (1.2–7.8)		
			≥ 1	81	4.8 (1.9–12.1)		
			Trend test *P* value, < 0.000 01				
			Mate consumption (women, L/day)			Age	
			Non-users	1	1.0		
			0.01–0.49	3	2.1 (0.1–31.7)		
			0.50–0.99	20	12.5 (2.0–80.1)		
			≥ 1	13	34.6 (4.9–246.5)		

CI, confidence interval; NR, not reported; SCC, squamous cell carcinoma; UADT, upper aerodigestive tract

to adjust for more variables, and provided further details regarding dose–response.

No studies were excluded from this review; however, where data from several studies were reported in a combined analysis, the results are reported for the combined analysis rather than for individual studies. In some instances (mostly in studies from Uruguay) it was difficult to judge whether newer, larger publications included all data from older publications or only partially used older data. Such instances are mentioned where appropriate.

The results of these studies are summarized below, first for cancer of the oesophagus and then for other cancers.

2.1.1 Cancer of the oesophagus

Nine independent case–control studies of mate and cancer of the oesophagus were available to the Working Group: Vassallo et al. (1985), Victora et al. (1987), De Stefani et al. (1990a), Castelletto et al. (1994), Rolón et al. (1995), Dietz et al. (1998), Sewram et al. (2003), Szymańska et al. (2010), and De Stefani et al. (2014). There were also two pooled analyses (Castellsagué et al., 2000; Lubin et al., 2014) that may include some additional cases and controls. A summary of these studies is outlined below.

Vassallo et al. (1985) conducted a case–control study of mate consumption and cancer of the oesophagus. This study included 226 cases and 469 controls enrolled between 1979 and 1984, all from the Oncology Institute of Montevideo, Uruguay. The controls were selected from similar populations seeking medical care in the same medical facilities for other neoplastic conditions such as cancers of the skin, colorectum, prostate (for men), and breast (for women). Controls were not matched to cases for age or sex. The age-adjusted odds ratios were 6.7 (95% CI, 4.0–11.3) and 34.6 (95% CI, 4.9–247) for men and women, respectively, with a consumption of mate > 1 L/day. After adjusting for age and tobacco and alcohol consumption, there was a significant ($P < 0.000\,01$) dose–response association between mate drinking and risk of cancer of the oesophagus in men, with an odds ratio of 4.8 (95% CI, 1.9–12.1) for consuming more than 1 L/day, compared with no consumption. [No data on temperature were reported.]

Four case–control studies published between 1987 and 1995 reported on studies carried out by the International Agency for Research on Cancer (IARC) in Brazil (Victora et al., 1987), Uruguay (De Stefani et al., 1990a), Argentina (Castelletto et al., 1994) and Paraguay (Rolón et al., 1995). Individual results for these studies are not reported here, as Castellsagué et al. (2000) published a pooled analysis of these four studies plus a fifth study that had not been published previously; the pooled analysis is described in the following.

Since the five studies analysed by Castellsagué et al. (2000) were all designed and conducted by IARC, they could be combined. Cases (n = 830) were patients with histologically confirmed squamous cell carcinomas of the oesophagus, selected from major hospitals. Cases and controls were enrolled between 1986 and 1992. Case participation rates ranged over 90–99% in each of these studies. Controls (n = 1779) were selected from the same hospitals and matched to cases for sex and age (± 5 years). The combined results showed an increased risk of squamous cell carcinoma for mate drinking (OR, 1.52; 95% CI, 1.10–2.12 for any consumption). An independent increased risk was associated with both quantity and temperature of mate consumed, even after adjustment for other major risk factors such as tobacco smoking and alcohol consumption. The overall adjusted odds ratio for mate temperature (very hot vs hot/warm/cold) was 1.89 (95% CI, 1.24–2.86) and for mate quantity (> 2 L/day vs none) was 3.04 (95% CI, 1.84–5.02). The joint effect of mate temperature and mate quantity showed a higher than multiplicative pattern, with a significant P value for interaction (0.02). There

was a statistically significant dose–response relationship for mate temperature ($P = 0.008$) and for mate quantity ($P = 0.0001$). [Regarding temperature, the odds ratio for drinking very hot mate was considerably greater than for drinking hot mate.]

Dietz et al. (1998) reported a case–control study of mate drinking and cancer of the oesophagus. The cases ($n = 55$) and controls ($n = 110$) were recruited between 1990 and 1991 from an endoscopy clinic in Rio Grande do Sul, Brazil. Controls were those who underwent endoscopy because of gastroenterological problems, but had no cancer. [This may be a concern, as controls may not be representative of the entire population for their mate drinking.] Controls were matched to cases for age and sex, but no further selection criteria were discussed. Questions were asked about age, sex, and consumption of alcohol, tobacco, mate, and other foods. The interviewer was blind to the case status of the study participants. No details were provided on definitions of amount, temperature, or frequency. The study found that drinking hot or very hot mate (vs "not hot") (OR, 2.55; 95% CI, 1.01–6.56) and daily intake of mate (OR, 5.58; 95% CI, 1.11–36.5) were associated with a higher risk of cancer of the oesophagus. [It is not clear whether these findings were adjusted for other risk factors; although the text states that multivariable analyses were performed, the covariates are not listed. A limitation of the study was that the controls were selected from a group of patients who underwent endoscopy.]

Sewram et al. (2003) published the results of a case–control study of mate consumption and squamous cell carcinoma (SCC) of the oesophagus. The cases ($n = 344$) and controls ($n = 469$) were recruited in Montevideo, Uruguay, from 1988 to 2000. The cases were histologically confirmed. The controls were selected from a variety of benign conditions and were matched to cases for sex, with a response rate of 93%. After adjusting for age, smoking, alcohol consumption, and several other factors, ever consuming mate was associated with a substantial increase in risk of squamous cell carcinoma (OR, 2.26; 95% CI, 1.19–4.27). High daily consumption (> 1 L/day) was associated with a higher risk (OR, 2.84; 95% CI, 1.41–5.73) compared with non-drinkers. Both temperature and amount of mate intake were significantly associated with higher risk of oesophageal squamous cell carcinoma. Among mate drinkers, consuming very hot mate (vs warm or hot) was associated with an increased risk (OR, 1.87; 95% CI, 1.17–3:00) after adjusting for amount of mate intake and several other risk factors. Likewise, those who consumed more than 1 L/day had a higher risk (OR, 1.62; 95% CI, 1.01–2.62) compared with those who drank between 0.1 L/day and 0.5 L/day. [There may be partial overlap between this study from 1998–1992 with one of the studies in Uruguay included in the combined analysis reported by Castellsagué et al. (2000).]

Szymańska et al. (2010) examined the association between mate drinking and cancer of the oesophagus as part of a large multicentre study of cancers of the upper aerodigestive tract in South America (seven cities in Argentina, Brazil, and Cuba); however, data from only four centres in Argentina and Brazil were used, as mate consumption was very low in other centres. The study included 80 cases of cancer of the oesophagus and 240 controls, frequency-matched to cases for sex, age, and centre. Participants were queried about ever use, amount, duration, and cumulative amount of mate drinking, as well as other variables such as smoking and alcohol drinking. After adjusting for important confounders such as age, sex, centre, smoking, and alcohol consumption, mate drinking was associated with an increased risk of cancer of the oesophagus with an odds ratio of 3.81 (95% CI, 1.75–8.30). There was a dose–response relationship for quantity of daily mate intake, as well as for duration of use and cumulative consumption. Compared with non-drinkers, an increased risk of cancer of the oesophagus was reported for

drinkers of cold/warm mate (OR, 7.52; 95% CI, 2.72–20.82) and drinkers of hot/very hot mate (OR, 3.33; 95% CI, 1.51–7.35).

De Stefani et al. (2014) published a study of diet and squamous cell carcinoma of the oesophagus, in which mate was also examined. Cases (n = 234) were diagnosed microscopically between 1996 and 2005 from patients referred to four major public health hospitals in Uruguay. Controls (n = 936) were selected from the same hospitals and in the same time period from patients with non-neoplastic conditions that were not etiologically related to smoking or alcohol drinking. Controls were frequency-matched to the cases for age (in 10-year periods), sex, and place of residence (Montevideo, other counties). After adjusting for major confounders, mate consumption (third tertile vs first tertile of mate years) was associated with a higher risk of oesophageal squamous cell carcinoma (OR, 2.04; 95% CI, 1.32–3.16). [It was unclear how much overlap exists between this study and those reported earlier (Sewram et al., 2003) or later (Lubin et al., 2014); the Working Group considered it most likely that these results were covered in the analyses by Lubin et al. (2014).]

Lubin et al. (2014) pooled data from the five IARC case–control studies described above (Castellsagué et al., 2000) and a case–control study from Uruguay to study the independent effect of cumulative use of mate and its temperature on the risk of squamous cell carcinoma of the oesophagus. The additional study from Uruguay was conducted within the Oncology Institute of Montevideo and cases were enrolled from 1988 to 2005. Controls were from the same institute, selected from diseases unrelated to smoking and alcohol consumption, and matched to cases for sex and age. A total of 1400 cases and 3229 controls were included. [There seemed to be substantial overlap for cases and controls for this study and those reported in Sewram et al. (2003) and De Stefani et al. (2014); only cases and controls recruited after 2000 may be new.] Overall, there was an increase in the odds ratio for ever versus never use of mate (OR, 1.60; 95% CI, 1.2–2.2). The pooled adjusted odds ratio for drinking warm, hot, and very hot mate (vs never drinkers) were 1.2 (95% CI, 0.8–1.7), 1.6 (95% CI, 1.2–2.2), and 2.2 (95% CI, 1.5–3.1), respectively, with a P value for trend of 0.01. The excess odds ratio (EOR) was calculated based on intensity, duration, and cumulative use of mate, and it was found that EOR was mainly a function of cumulative use as measured by litres consumed per day × years of drinking (LPDY). After considering cumulative use, whether the mate consumer demonstrated high-intensity/short-duration or low-intensity/long-duration use had no effect on the results. The EOR for LPDY varied by temperature of use: EOR/LPDY estimates for consumption of warm, hot, and very hot mate were 0.004 (95% CI, 0.002–0.013), 0.007 (95% CI, 0.003–0.013), and 0.016 (95% CI, 0.009–0.027), respectively, and differed significantly (P < 0.01). There was a significant interaction (P = 0.02) between mate consumption and smoking, and the exposure–response relationship was strongest in never smokers of tobacco (EOR/LPDY, 0.018; 95% CI, 0.007–0.038). [This pooled analysis included all of the studies described above except Vassallo et al. (1985), Dietz et al. (1998), and Szymańska et al. (2010), which were not from Uruguay.]

2.1.2 Other cancers

Mate drinking has been studied in relation to cancers at several sites, including the upper aerodigestive tract (oral cavity, pharynx, hypopharynx, and larynx), lung, stomach, colon, rectum, kidney, bladder, prostate, and breast. Nearly all studies are hospital-based case–control studies, in which cases are histologically diagnosed. In general, participation rates for cases and controls are very high (> 90%). Data are typically available for major confounders, such as age, sex, place of residence, tobacco consumption, and alcohol consumption, and these factors

are adjusted for. All of the data come from South America, in particular from Uruguay where several case–control studies have been conducted for mate and a host of cancers. These studies are summarized below by cancer site.

(a) Cancers of the upper aerodigestive tract

De Stefani et al. (1987) reported the results of a case–control study of 107 patients with cancer of the larynx and 290 controls from the University Hospital of Montevideo, Uruguay. Cases were those identified between 1985 and 1986; controls were those with diseases considered not related to tobacco and alcohol, chosen from the same hospital for the same time period. Data were collected on demographic variables, tobacco and alcohol consumption, consumption of several food items, mate drinking, and other covariates. Mate drinking was associated with a 3-fold increased risk of cancer of the larynx, with an odds ratio of 3.4 (95% CI, 1.8–6.6) after controlling for the effects of age and tobacco and alcohol consumption.

De Stefani et al. (1988) reported the results of a case–control study of 108 cases of cancers of the oropharynx and 286 controls, also in Montevideo, Uruguay, with a similar design and methods, and restricted to men. Patients diagnosed with cancers of the lip, salivary gland, and nasopharynx were excluded. Mate exposure showed a significant dose–response association with risk of cancer of the oropharynx. After adjustment for age and tobacco and alcohol intake, drinking 1.00–1.99 L/day and > 2 L/day compared with drinking < 1 L/day of mate was associated with a relative risk of 2.5 (95% CI, 1.1–5.7) and 5.2 (95% CI, 2.1–13.1), respectively.

Franco et al. (1989) reported on the results of the association between mate intake and oral cavity cancers (carcinomas of the tongue, gum, floor, and other parts of the mouth). This case–control study was conducted in three metropolitan areas in Brazil (São Paulo), Curitiba, and Goiânia between 1986 and 1988. Interviews were conducted with 232 cases and 464 hospital non-cancer controls matched for 5-year age group, sex, hospital catchment area, and trimester of admission. After adjusting for tobacco and alcohol consumption, compared with drinking < 1 cup of mate per month, drinking 1–30 cups/month and > 30 cups/month was associated with odds ratios of 1.6 (95% CI, 0.8–3.3) and 1.6 (95% CI, 0.8–3.3), respectively. Most of the increased risk was seen for cancer of the tongue.

Oreggia et al. (1991) published the results of a study on mate consumption and cancer of the tongue in men. The study involved interviews with 57 cases and 353 controls identified in 1987–1989. All cases were squamous cell carcinomas. The design and methods were similar to those of De Stefani et al. (1987). Compared with consuming mate at < 1 L/day, consuming more than 2 L/day was associated with an increased risk with a crude odds ratio of 2.5 (95% CI, 1.2–5.6). After adjusting for age and tobacco use, this odds ratio was reduced to 1.8 [no confidence intervals reported. Further adjustment for other variables (e.g. alcohol drinking) was not reported.]

Pintos et al. (1994) reported on a case–control study of cancers of the upper aerodigestive tract in relation to mate drinking. Cases (n = 378) were all newly diagnosed patients with cancers of the mouth, pharynx, and larynx referred to Erasto Gaertner Hospital, Brazil, between 1987 and 1989. Controls (n = 756) were selected from this hospital or another general hospital in the same city, and matched to cases (2 : 1) for sex, age (5-year groups), and trimester of admission. Data were available for mate drinking and intensity of consumption, as well as for other potential confounders including tobacco and alcohol consumption. After adjusting for potential confounders, the odds ratio was 1.6 (95% CI, 1.2–2.2). The excess risk was mainly seen for cancers of the oral cavity (OR, 1.9; 95% CI, 1.1–3.3) and larynx (OR, 2.2; 95% CI, 1.1–4.5), but not cancer of the pharynx. There was a clear

dose–response pattern for all cancers combined (*P* for trend = 0.001) and for cancers of the oral cavity and larynx.

As part of their multisite study of mate and cancers of the upper aerodigestive tract, Szymańska et al. (2010) reported results on 628 cases of cancer of the oropharynx, 410 cancers of the hypopharynx and larynx, and 1026 controls. The design was described earlier in Section 2.1.1. Controls were frequency-matched to cases for sex, age, and centre. Participants were questioned on ever use, amount, duration, and cumulative amount of mate drinking as well as on other variables such as smoking and alcohol consumption. After adjusting for important confounders, ever drinking mate was associated with an increased risk of cancers of the oral cavity and oropharynx (OR, 1.48; 95% CI, 1.05–2.08) and hypopharynx and larynx (OR, 1.51; 95% CI, 1.05–2.18). There was some evidence of a dose–response relationship with cumulative use (litres per lifetime), which was marginally significant (*P* for trend, 0.08 and 0.07, for cancers of the oral cavity and oropharynx, and hypopharynx and larynx, respectively). There was no clear association with temperature of mate intake; in fact, the odds ratios were higher for cold/warm mate than hot/very hot mate (2.89 vs 1.15 for cancers of the oral cavity and oropharynx, and 2.33 vs 1.28 for cancers of the hypopharynx and larynx). When the study was limited to people who never smoked or drank (37 cases and 176 controls), ever drinking mate was associated with an increased risk of all cancers of the upper aerodigestive tract with an odds ratio of 2.81 (95% CI, 1.08–7.34). [These results are consistent with the findings of Lubin et al. (2014), in that associations were seen for non-smokers and non-drinkers.]

Deneo-Pellegrini et al. (2013) reported on a case–control study of mate drinking and squamous cell cancers originating from the oral cavity based on a reanalysis of data presented in a previous study (De Stefani et al., 2011). The cases (n = 696) and controls (n = 696) were all men, selected from the Cancer Institute of Montevideo, Uruguay, between 1990 and 2001. Controls were selected from conditions not related to tobacco smoking or alcohol consumption, and were frequency-matched to cases for age and place of residence. In analyses adjusted for main confounders such as tobacco and alcohol consumption, the odds ratio was 1.15 (95% CI, 0.76–1.73). There was highly significant (P < 0.001) interaction between the mate consumption variables and alcohol and tobacco use. [Some aspects of the analysis were unclear; for example, the interaction terms were not fully shown. The results are at least partially included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(b) Cancer of the lung

De Stefani et al. (1996) conducted a case–control study of mate consumption in relation to cancer of the lung. Cases were 497 men admitted to the Oncology Institute of Montevideo, Uruguay, from 1988 to 1994. Controls (n = 497) were from those admitted to the same hospital, and were frequency-matched to cases for age and place of residence. Controls were selected from among non-neoplastic conditions, or cancers that were deemed to be unrelated to mate consumption (e.g. cancer of the prostate). After adjusting for potential confounders including pack-years of cigarette smoking, mate drinking was associated with a higher risk of cancer of the lung with an odds ratio of 2.4 (95% CI, 1.3–4.3). There was a statistically significant dose–response relationship with intensity (litres per day) (P < 0.001), duration (P = 0.005), and cumulative use (P = 0.001). This association was strongest for small cell lung cancer but virtually non-existent for adenocarcinoma of the lung. [The results may have been partially included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(c) Cancer of the stomach

De Stefani et al. (1990b) conducted a case–control study of mate drinking and gastric cancer. The cases (n = 210) and controls (n = 630) were selected from those admitted to the University Hospital of Montevideo, Uruguay, during July 1985–December 1988. Cases and controls received the same detailed questionnaire from three social workers who were unaware of the objectives of the study. Mate ingestion was associated with an increased risk of cancer of the stomach in both sexes. After adjusting for age, sex, smoking duration, wine ingestion, and place of residence, compared with drinking mate at < 1 L/day, drinking 1–1.99 L/day and ≥ 2 L/day was associated with relative risks of 1.0 (95% CI, 0.1–1.5) and 2.7 (95% CI, 1.7–4.2), respectively.

(d) Cancer of the kidney

De Stefani et al. (1998) conducted a case–control study of mate drinking and renal cell carcinoma with 121 histologically verified cases admitted to a hospital in Montevideo, Uruguay, between 1988 and 1995. Controls (n = 243) were selected from the same institution, from patients who did not have any malignancy or conditions assumed to be related to mate consumption. Controls were frequency-matched to cases (2 : 1) for age, sex, and place of residence. After adjusting for potential confounders, ever drinking mate was associated with a non-significant increased risk of renal cell carcinoma with an odds ratio of 1.6 (95% CI, 0.7–3.3). There was a dose–response relationship with intensity (P = 0.003), duration (P = 0.07), and cumulative use (P = 0.02) of mate. For example, those who consumed more than 2 L of mate per day had an increased risk with an odds ratio of 3.1 (95% CI, 1.3–7.9). [The results may be partially included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(e) Cancer of the bladder

Iscovich et al. (1987) conducted a study of several risk factors, including mate drinking, in relation to cancer of the bladder in Argentina. A total of 117 cases of cancer of the bladder, 117 hospital controls, and 117 neighbourhood controls were enrolled in this study. All cases were histologically confirmed, and 93% were transitional cell carcinomas. Controls were matched to cases for sex and age. Cases and controls were recruited from patients during the period 1983–1985. Of these, 99 cases and 198 controls were included in the mate analysis. After adjusting for age and cigarette smoking, the odds ratios for mate drinking were 2.0, 0.9, and 0.8 for drinking < 10 drinks, 10–19 drinks, and ≥ 20 drinks per day compared with not drinking any mate. [No confidence intervals were provided. The Working Group estimated P for trend = 0.05, suggestive of a negative trend.]

De Stefani et al. (1991) reported a case–control study of mate drinking and transitional cell carcinoma of the bladder. The cases (n = 111) comprised patients newly diagnosed between 1987 and 1989 in two major hospitals in Montevideo, Uruguay. The controls (n = 222) were selected from patients from the same hospitals with conditions unrelated to tobacco smoking, and were matched to cases by age and sex. A strong dose–response association was observed between mate drinking and cancer of the bladder, even after adjusting for sex, age, and tobacco consumption. For example, when analysis was limited to men and adjusted for age, place of residence, social class, and type and duration of tobacco use, compared with those who consumed < 0.5 L of mate per day, those who consumed increasingly higher amounts per day had odds ratios of 3.3 (95% CI, 0.6–19.3) for 0.5–0.99 L/day, 5.2 (95% CI, 0.9–29.3) for 1.0–1.9 L/day, and 7.2 (95% CI, 1.2–41.6) for ≥ 1.5 L /day, with a P value for the trend of 0.004. The joint association of tobacco and mate with bladder cancer followed a multiplicative model.

De Stefani et al. (2007) reported the results of another hospital-based case–control study of transitional cell carcinoma of the bladder and mate drinking. Incident cases (n = 255) were recruited from patients diagnosed in one of the four major hospitals in Montevideo, Uruguay, during 1996–2000. Controls (n = 501) were selected over the same time period and in the same hospitals from patients with diseases not related to tobacco smoking or alcohol drinking and without recent changes in their diet. Controls were frequency-matched to cases for age, sex, and place of residence. Data on mate consumption were obtained by interview. Ever drinking mate was associated with an increased risk of cancer of the bladder, with an adjusted odds ratio of 2.2 (95% CI, 1.2–3.9). Intensity (litres per day) ($P < 0.01$), duration ($P < 0.01$), and cumulative consumption ($P < 0.01$) showed a dose–response relationship. There was also evidence of a trend of risk increasing with temperature (P for trend not reported). Compared with non-drinkers, those who drank mate warm, hot, and very hot had odds ratios of 2.1 (95% CI, 0.8–5.4), 2.1 (95% CI, 1.2–3.7), and 4.9 (95% CI, 2.2–11), respectively. [The results were possibly included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

Bates et al. (2007) published findings from a case–control study of mate consumption in relation to transitional cell carcinoma of the bladder. The cases (n = 114), identified by pathologists and urologists, were enrolled during 1996–2000 from patients resident in the counties of Union and Marcos Juarez, Cordoba Province, Argentina; all were histologically confirmed. Controls (n = 114) (matched according to county of residence, sex, and year of birth) were identified from voter registration lists. Data regarding consumption of beverages, smoking, and occupational and medical histories were collected by questionnaire. Separate questions concerned consumption of mate *con bombilla* and mate *cocido*. There was no overall association between mate *con bombilla* or *cocido* consumption at the time of interview, 20 years before the interview, or 40 years before the interview and risk of cancer of the bladder in analyses that controlled for smoking status, sex, and year of birth. The only significant association (OR, 3.77; 95% CI, 1.17–12.1) was for those who consumed mate *con bombilla* 20 years before the interview and were ever smokers.

(f) Cancer of the prostate

Deneo-Pellegrini et al. (2012) reported a case–control study of mate drinking and cancer of the prostate. Cases (n = 326) were recruited from four major hospitals in Montevideo, Uruguay, between 1996 and 2004. Controls (n = 652) were selected from patients from the same hospitals with diseases not related to smoking or drinking. Those with a recent dietary change were excluded. Controls were frequency-matched to cases according to age and place of residence. A detailed questionnaire was completed for both cases and controls during a face-to-face interview. After adjusting for age, place of residence, urban/rural status, education, family history of prostate cancer among first-degree relatives, body mass index, and total energy intake, mate intake was associated with a higher risk of cancer of the prostate. Compared with the first tertile, the second and third tertiles of use were associated with odds ratios of 1.40 (95% CI, 0.87–2.26) and 1.96 (95% CI, 1.17–3.31), respectively, with a P value for trend of 0.005. [The results were possibly included in the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(g) Cancer of the breast

Ronco et al. (2016) combined the results of two case–control studies from two hospitals in Uruguay. The overall design of this study was similar to other studies on mate from Uruguay, with cases and controls from the same hospitals and matched for age and residence. All cases and

controls were women. A total of 572 incident cases of cancer of the breast and 889 controls were interviewed with a questionnaire. After adjusting for multiple risk factors for breast cancer, odds ratios for increasing cumulative dose of mate (litres consumed per day × years of drinking) were 0.74 (95% CI, 0.51–1.07), 0.68 (95% CI, 0.47–0.98), and 0.50 (95% CI, 0.34–0.73), suggesting an inverse association between mate drinking and risk of cancer of the breast (*P* for trend < 0.001). [The data seemed to be a subsample of the multisite study by De Stefani et al. (2011). See Section 2.1.2 (h) 'Cancer at multiple sites' below.]

(h) Cancer at multiple sites

De Stefani et al. (2011) published the results of their case–control study of mate drinking in relation to cancers arising from 13 sites (mouth, pharynx, oesophagus, stomach, colon, rectum, larynx, lung, female breast, cervix uteri, prostate, bladder, and kidney). The study was conducted between 1990 and 2004 and included cases (*n* = 8875) selected from the four major hospitals in Montevideo, Uruguay. The numbers for each cancer site were 360 mouth, 424 pharynx, 605 oesophagus, 408 stomach, 334 colon, 428 rectum, 554 larynx, 2045 lung, 2061 female breast, 233 cervix uteri, 720 prostate, 429 bladder, and 274 kidney. Controls (*n* = 4326) were drawn from the same hospitals and the same time period and included patients with non-neoplastic conditions, unrelated to tobacco smoking or alcohol drinking, and without recent changes in their diets. Odds ratios and 95% confidence intervals were estimated using polytomous multiple regressions. Compared with not drinking any mate, drinking > 2 L/day was associated with an increased risk of cancers of the bladder (OR, 3.88; 95% CI, 2.47–6.08; *P* for trend < 0.0001), oesophagus (OR, 3.09; 95% CI, 1.95–4.91; *P* for trend < 0.0001), kidney (OR, 2.27; 95% CI, 1.39–3.72; *P* for trend < 0.0001), cervix uteri (OR, 2.1; 95% CI, 1.19–3.72; *P* for trend < 0.0001), lung (OR, 1.99; 95% CI, 1.55–2.58; *P* for trend < 0.0001), prostate (OR, 1.73; 95% CI, 1.22–2.45; 0.003), larynx (OR, 1.54; 95% CI, 1.03–2.32; *P* for trend = 0.06), and stomach (OR, 1.52; 95% CI, 1.01–2.29; *P* for trend = 0.02). In contrast, mate drinking was not associated with a higher risk of cancers of the mouth, pharynx, colon, rectum, or female breast. Hot mate drinking was significantly associated with an increased risk of cancers of the upper aerodigestive tract (OR, 1.41; 95% CI, 1.12–1.79; *P* = 0.0001), larynx (OR, 1.57; 95% CI, 1.07–2.31; *P* = 0.001), lung (OR, 1.95; 95% CI, 1.53–2.49; *P* < 0.0001), prostate (OR, 1.58; 95% CI, 1.18–2.13; *P* = 0.002), bladder (OR, 2.42; 95% CI, 1.58–3.69; *P* < 0.0001), and kidney (OR, 1.96; 95% CI, 1.22–3.14; *P* = 0.004) when compared with non-drinkers.

Combining all cancers included in this analysis, compared with non-drinkers odds ratios were 1.30 (95% CI, 1.14–1.47) for drinking < 1 L/day, 1.38 (95% CI, 1.22–1.56) for drinking 1 to < 2L/day and 1.50 (95% CI, 1.30–1.72) for drinking ≥ 2 L/day (*P* for trend < 0.0001). Combining all sites, odds ratios were 1.22 (95% CI, 1.07–1.39) for drinking warm mate and 1.46 (95% CI, 1.29–1.66) for drinking hot mate (*P* for trend < 0.0001).

2.2 Very hot beverages other than mate

Since the previous review of the carcinogenicity of coffee, tea, and mate (IARC, 1991), additional studies have reported data on the association between beverage temperature and risk of cancer. These studies concerning hot beverages other than mate are reviewed in this section. Studies on the association between hot mate drinking and cancer are described in Section 2.1.

The majority of studies of the association between drinking very hot beverages other than mate and cancer have focused on cancer of the oesophagus. The evidence is therefore reviewed in two sections: one on cancer of the oesophagus

(Section 2.2.1), and a second including all other cancers (Section 2.2.2). Beverage temperature was typically assessed through questions about participants' subjective perception of temperature. In this review, studies in which the reference group consisted only of those who did not drink the beverage of interest were given lower weight, except when two or more categories of beverage temperature were separately compared with this reference group, as this would allow risk estimates of drinking low- and high-temperature beverages to be compared.

2.2.1 Cancer of the oesophagus

See Table 2.2.

(a) Very hot tea and cancer of the oesophagus

One cohort study, 15 case–control studies, and a pooled analysis of multiple case–control studies that investigated the association between very hot tea and cancer of the oesophagus were available to the Working Group. The studies that reported results only for tea combined with other beverages are discussed in Section 2.2.1 (c).

(i) Cohort study

Kinjo et al. (1998) reported results of a prospective study of 220 272 individuals (aged 40–69 years at the baseline) in 29 public health districts in 6 prefectures in Japan. The participants were recruited in 1965 and followed up until 1981. A total of 440 deaths from cancer of the oesophagus were identified from the follow-up period of 1966–1981. Drinking hot tea (vs non-hot tea) was associated with the risk of death from cancer of the oesophagus (OR, 1.5; 95% CI, 1.1–1.9) in analyses that controlled for age, occupation, sex, locality (prefecture), green and yellow vegetable consumption, alcohol consumption, and tobacco use.

(ii) Case–control studies

Kaufman et al. (1965) studied 82 cases of cancer of the oesophagus and 73 controls in Kazakhstan, former Soviet Union, and later added 51 cases from another area. Finally, 127 cases and 72 controls were included in the analysis. Drinking (vs not drinking) very hot tea was associated with a higher risk of cancer of the oesophagus [crude OR, 3.18; 95% CI, 1.60–6.48]. In the same region, Bashirov et al. (1968) compared tea-drinking habits in 301 cases of cancer of the oesophagus (142 men and 159 women) and 301 healthy population controls. Cancer of the oesophagus was more common among those who reported drinking ≥ 7 cups of hot black tea at a single sitting than others [OR, 2.6; $P < 0.01$ in men; OR, 3.2; statistically non-significant in women]. Neither study adjusted for smoking, alcohol, or any other risk factors; however, in the study by Bashirov et al. (1968), duration of smoking and the amount of nass use (a smokeless tobacco product) in cases and controls were comparable. [The Working Group noted that it was unclear whether or not the reference groups in these two studies included those who did not drink the beverage of interest.]

De Jong et al. (1974) reported results of a hospital-based case–control study of cancer of the oesophagus among Singaporeans conducted in 1970–1972. For the 131 cancer cases included in this study (95 men and 36 women), 345 controls from non-cancer patients from the same ward and 320 controls from orthopaedic patients from a general hospital were recruited, matching for age and sex. In this study, drinking "burning hot" tea, coffee, and barley (compared with not drinking these hot drinks) was associated with a statistically significant increased risk of cancer of the oesophagus in both men and women in analyses that were only adjusted for dialect group. In the multivariate models that were adjusted for several potential confounding factors, including smoking and alcohol drinking, the authors used

Table 2.2 Epidemiological studies on cancer of the oesophagus and drinking very hot beverages other than mate

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tran et al. (2005) Linxian, China 1986–2001 Cohort	29 584 adults with no history of cancer from the general population Exposure assessment method: questionnaire (all study participants were interviewed to complete a baseline questionnaire in 1984)	Oesophagus (SCC)	Hot liquid (in summer) 0 time/year ≥ 1 Hot liquid (in winter) 0 time/year ≥ 1	 NR NR NR NR	 1.00 0.96 (0.87–1.07) 1.00 0.95 (0.87–1.04)	Age and sex	Strengths: prospective design; results for at least one specified histological subtype Limitations: the number of cases in each category of exposure was not reported
Kaufman et al. (1965)[a] Kazakhstan, former Soviet Union NR Case–control	Cases: 127 Controls: 72 Exposure assessment method: questionnaire	Oesophagus	Tea temperature Does not drink hot tea Drinks hot tea	 64 63	 1.00 [3.18 (1.60–6.48)]	None	The *P* value for the association was < 0.001. Limitations: no adjustments for some major risk factors of oesophageal cancer, notably smoking

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bashirov et al. (1968)[b] Kazakhstan, former Soviet Union NR Case–control	Cases: 301 Controls: 301 Exposure assessment method: questionnaire	Oesophagus	Glasses of hot tea at a time (men) < 7 ≥ 7 Glasses of hot tea at a time (women) < 7 ≥ 7	 NR NR NR NR	 1.00 [2.6] 1.00 [3.2]		The *P* value for the association in men was < 0.01. The association was not statistically significant in women. Limitations: no adjustments for some major risk factors of oesophageal cancer, notably smoking; however, duration of smoking and the amount of nass use (a chewing tobacco product) in cases and controls were comparable
De Jong et al. (1974) Singapore 1970–1972 Case–control	Cases: 131 patients admitted for dysphagia/weight loss who had an oesophageal tumour in radiographies; adenocarcinoma and cardia tumours excluded Controls: 665, 2 per case from the same ward as the case and 2 per case from orthopaedic units of one hospital, matched for sex and age Exposure assessment method: questionnaire	Oesophagus	Beverage temperature (men) Per unit temperature score Trend test *P* value, 0.01 Beverage temperature (women) Per unit temperature score Trend test *P* value, 0.01	 95 36 	 [2.10 (1.83–2.40)] [2.47 (1.87–3.26)] 	Birthplace, dialect group, education, smoking, alcohol drinking, and intake of bread, potatoes, and bananas	82% of cases histologically confirmed Limitations: results from multivariate analyses reported only for a combination of three types of hot beverages, not for individual beverages

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cook-Mozaffari et al. (1979) Islamic Republic of Iran 1975–1976 Case–control	Cases: 344 from Caspian Cancer Registry, northern Islamic Republic of Iran; 4% confirmed histologically Controls: 688 randomly selected from the same village or town as cases; individually matched for age, sex, and place of residence Exposure assessment method: questionnaire	Oesophagus	Tea temperature (men) Non-hot Hot Tea temperature (women) Non-hot Hot	 NR NR NR NR	 1.00 1.72 1.00 2.17	Full account of matching was taken in the presented results	Limitations: Proxy interviews for about 20% of cases. No adjustments for some major risk factors of oesophageal cancer, notably smoking. However, alcohol drinking in both sexes and smoking in women were uncommon habits in this study
Gao et al. (1994) Shanghai, China 1990–1993 Case–control	Cases: 902 from Shanghai Cancer Registry Controls: 1552 from population (Shanghai Resident Registry) Exposure assessment method: questionnaire	Oesophagus	Soup or porridge temperature (men only) Cold/neither cold nor hot Hot Burning hot Trend test *P* value, 0.001 Soup or porridge temperature (women only) Cold/neither cold nor hot Hot Burning hot Trend test *P* value, 0.001	 NR NR NR NR NR NR	 1.00 1.21 (0.88–1.66) 4.75 (3.33–6.79) 1.00 1.90 (1.29–2.79) 6.77 (4.09–11.20)	Age, education, birthplace, tea drinking, cigarette smoking, alcohol drinking, and consumption of preserved foods, vegetables, and fruit	Part of a larger study of cancers of the oesophagus, pancreas, colon, and rectum Strengths: large sample size Limitations: the number of cases in each category of soup/ porridge temperature was not reported

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Launoy et al. (1997) France, three regions 1991–1994 Case–control	Cases: 208 men admitted to university hospitals; histologically confirmed Controls: 399 men admitted to the same hospitals in rheumatology, orthopaedics, or ophthalmology units; matched for hospital and age Exposure assessment method: questionnaire	Oesophagus (SCC)	Cold calvados (calvados drunk alone, g alcohol/week)			Age, residence, occupation, education, marital status, smoking, interviewer, intake of total and specific alcoholic drinks	It would be difficult to separate the effect of temperature from that of alcohol on development of oesophageal cancer Strengths: results for at least one specified histological subtype Limitations: men only
			Non-drinker	195	1.00		
			1–5	9	1.01 (0.37–2.74)		
			≥ 6	4	0.86 (0.20–3.78)		
			Hot calvados (calvados drunk with coffee, g alcohol/week)				
			Non-drinker	124	1.00		
			1–20	24	1.40 (0.67–3.92)		
			21–40	8	1.40 (0.39–5.08)		
			≥ 41	52	2.33 (1.12–4.87)		
			Trend test *P* value, < 0.05				
			Cold spirits (spirits drunk alone, g alcohol/week)				
			Non-drinker	130	1.00		
			1–5	44	0.73 (0.42–1.27)		
			6–10	13	0.68 (0.28–1.62)		
			≥ 11	21	0.76 (0.36–1.61)		
			Hot spirits (spirits drunk with hot water or coffee, g alcohol/week)				
			Non-drinker	163	1.00		
			1–5	14	0.80 (0.33–1.94)		
			6–10	5	1.65 (0.37–7.33)		
			≥ 11	26	1.83 (0.91–4.31)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Garidou et al. (1996) Athens, Greece 1989–1991 Case–control	Cases: 99 (43 SCC, 56 adenocarcinoma) from nine collaborating hospitals; cases were histologically confirmed Controls: 200 Athens residents hospitalized for injury; individually matched for age and sex Exposure assessment method: questionnaire	Oesophagus (SCC)	Temperature preference for beverages and foods			Age, sex, birthplace, education, height, analgesics, coffee drinking, tobacco and alcohol use, and energy intake	Strengths: results for at least one specified histological subtype Limitations: small sample size
			Cold	30	1.00		
			Hot or very hot	13	1.89 (0.80–4.49)		
			Trend test *P* value, 0.15				
		Oesophagus (adenocarcinoma)	Temperature preference for beverages and foods				
			Cold	41	1.00		
			Hot or very hot	15	1.82 (0.85–3.91)		
			Trend test *P* value, 0.13				
Kinjo et al. (1998) Japan 1966–1981 Cohort	220 272 individuals from 29 public health districts in 6 prefectures Exposure assessment method: questionnaire	Oesophagus	Tea temperature			Age, sex, prefecture, occupation, green-yellow vegetable intake, and tobacco and alcohol use	Strengths: prospective design Limitations: data on histology were not available
			Not hot	344	1.00		
			Hot	96	1.5 (1.1–1.9)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Castellsagué et al. (2000) Uruguay, Argentina, Brazil, Paraguay 1985–1992 Case–control	Cases: 830 from hospitals and clinics in each study area (La Plata, Argentina; Porto Alegre and Pelotas, Brazil; Asuncion, Paraguay; Montevideo, Uruguay); histologically confirmed Controls: 1779 patients admitted to the same hospital during the same period as the cases and matched for sex and age Exposure assessment method: questionnaire	Oesophagus (SCC)	Coffee temperature			Age, sex, prefecture, occupation, green-yellow vegetable intake, and tobacco and alcohol use	Strengths: pooled analysis of several studies with a large sample size; results for at least one specified histological subtype Limitations: small number of tea drinkers in this study
			Cold–warm	48	1.00		
			Hot	146	0.54 (0.33–0.87)		
			Very hot	34	1.01 (0.52–1.98)		
			Trend test *P* value, 0.6				
			Any very hot beverage (including mate)				
			Never very hot	554	1.00		
			Ever very hot	135	2.07 (1.55–2.76)		
			Any very hot beverage (other than mate)				
			Never very hot	404	1.00		
			Ever very hot	90	2.45 (1.72–3.49)		
			Tea temperature			Age group, sex, hospital, residency, years of education, average number of cigarettes/day, and average amount of pure ethanol/day	
			Cold–warm	27	1.00		
			Hot	51	0.66 (0.35–1.25)		
			Very hot	20	3.73 (1.41–9.89)		
			Trend test *P* value, 0.11				
			Coffee with milk temperature				
			Cold–warm	72	1.00		
			Hot	206	0.89 (0.62–1.29)		
			Very hot	64	2.29 (1.37–3.81)		
			Trend test *P* value, 0.009				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cheng et al. (2000) England and Scotland 1993–1996 Case–control	Cases: 74 women with oesophageal cancer living in the study areas at the time of diagnosis Controls: 74 from population health registers; matched to cases by age and general practice Exposure assessment method: questionnaire	Oesophagus (adenocarcinoma)	Tea or coffee temperature Warm Hot Very/burning hot Trend test *P* value, 0.202	 20 42 12	 1.00 0.75 (0.32–1.76) 0.51 (0.18–1.45)	None	Only female participants Strengths: results for at least one specified histological subtype Limitations: small sample size
Nayar et al. (2000) New Delhi, India 1994–1997 Case–control	Cases: 150 outpatient and inpatient admissions in one hospital; histologically confirmed with no previous treatment Controls: 150 apparently healthy attendees to the same hospital as cases Exposure assessment method: questionnaire	Oesophagus	Tea temperature Warm Hot Burning hot	 40 78 29	 1.00 1.11 (0.62–1.96) 1.27 (0.60–2.69)	None	Possible overlap with Srivastava et al. (1995, 1997)

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sharp et al. (2001) England and Scotland 1993–1996 Case–control	Cases: 159 women, histologically confirmed Controls: 159 women from population; individually matched by age and general practice Exposure assessment method: questionnaire	Oesophagus (SCC)	Tea or coffee temperature Very/burning hot Hot Warm Trend test *P* value, 0.03	 50 81 25	 1.00 0.75 (0.38–1.47) 0.34 (0.13–0.88)	Slimming diet, breakfast, salad, smoking, aspirin use, centre-aspirin interaction	Only female participants Strengths: Results for at least one specified histological subtype
Terry et al. (2001) Sweden 1995–1997 Case–control	Cases: 356 from Swedish population < 80 years of age; histologically confirmed Controls: 815 from Swedish population; frequency matched on age and gender Exposure assessment method: questionnaire	Oesophagus (adenocarcinoma)	Tea or coffee temperature None, cold, lukewarm Hot Very hot Trend test *P* value, 0.13	 NR NR NR	 1.00 0.7 (0.5–1.1) 0.6 (0.3–1.3)	Age, sex, BMI, smoking, gastro-oesophageal reflux symptoms, alcohol intake, fruit, vegetable, and energy consumption, frequency of hot beverages	Cases included 167 SCC and 189 adenocarcinoma of the oesophagus Strengths: nationwide study; results for at least one specified histological subtype Limitations: the question on temperature concerned hot beverages 20 years before interview
		Oesophagus (SCC)	Tea or coffee temperature None, cold, lukewarm Hot Very hot Trend test *P* value, 0.77	 NR NR NR	 1.00 1 (0.6–1.6) 0.8 (0.4–1.8)		
Zhang et al. (2001) Guangdong Province, China 1999 Case–control	Cases: 214 Controls: 214; matched for sex, age, and residential locations Exposure assessment method: questionnaire	Oesophagus	Tea temperature Did not drink hot tea regularly Regular hot tea drinking	 116 98	 1.00 2.28 (1.39–3.74)	Cooking oil from pork fat, drinking tap water, regular meat eating, eating quickly, eating hard foods	Ever-smoking did not show a statistically significant association with oesophageal cancer risk in unadjusted models, and it was not included in multivariate analysis

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Onuk et al. (2002) Turkey, Erzurum 1999–2000 Case–control	Cases: 44 from one hospital; histologically confirmed Controls: 100 hospital patients with no dyspeptic symptoms Exposure assessment method: questionnaire	Oesophagus	Tea temperature Other Hot (Kitlama) Trend test *P* value, 0.001	 3 41	 1.0 8.7 (2.5–30.2)	Unclear in the article	Results may have been adjusted for tobacco use, fruit, vegetable, coffee, and pickle intake, and type of bread Limitations: small sample size; information on adjustments is unclear, no information on subtypes
Hung et al. (2004) Taiwan, China 1996–2002 Case–control	Cases: 365 histologically confirmed Controls: 532 individually matched for age and hospitalization date Exposure assessment method: questionnaire	Oesophagus (SCC)	Hot drink or soup consumption (at age 20–40 years) < 3 times/day ≥ 3 Hot drink or soup consumption (at age ≥ 40 years) < 3 times/day ≥ 3	 181 86 179 93	 1.0 1.8 (1.1–3.0) 1.0 1.3 (0.8–2.1)	Age, education, ethnicity, source of hospital, smoking, alcohol drinking, and areca nut chewing	Only male participants; Chen et al. (2009) may provide results from this population with an extended recruitment period Strengths: results for at least one specified histological subtype
Chen et al. (2009) Taiwan, China 1996–2005 Case–control	Cases: 343 from three medical centres; histologically confirmed Controls: 755 from same hospitals; matched for age Exposure assessment method: questionnaire	Oesophagus (SCC)	Hot drink or soup < 1 time/day ≥ 1	 48 226	 1.0 0.8 (0.5–1.4)	Age, education levels, ethnicity, source of hospital, smoking, alcohol drinking, and areca nut chewing	This study may provide results from an extended recruitment period of Hung et al. (2004) study Strengths: results for at least one specified histological subtype

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Yokoyama et al. (2006) Japan 2000–2004 Case–control	Cases: 52 from four hospitals; histologically confirmed Controls: 412 cancer-free women who visited clinics for health check-ups Exposure assessment method: questionnaire	Oesophagus (SCC)	Hot food or drink preference			Age	Only women Strengths: results for at least one specified histological subtype Limitations: small sample size; no adjustments for smoking or alcohol drinking
			Dislike very much	1	1.00		
			Dislike somewhat	1	0.21 (0.01–3.60)		
			Neither like or dislike	25	1.00 (0.12–8.17)		
			Like somewhat	15	1.53 (0.18–12.92)		
			Like very much	10	3.43 (0.39–30.46)		
			Trend test *P* value, 0.0011				
Islami et al. (2009a) Islamic Republic of Iran; Golestan Province 2003–2007 Case–control	Cases: 300 patients referring to the only gastrointestinal specialty clinic in the study area; histologically confirmed Controls: 571 population-based; individually matched or by neighbourhood of residence, age, and sex Exposure assessment method: questionnaire	Oesophagus (squamous cell carcinoma)	Tea temperature			Ethnicity, alcohol intake, vegetable intake, tobacco or opium use, rural residence, education, car ownership, and black and green tea consumption	Good agreement between questions Strengths: Information on temperature and the interval between pouring and drinking; results for at least one specified histological subtype; high participation
			Warm or lukewarm	127	1		
			Hot	108	2.07 (1.28–3.35)		
			Very hot	63	8.16 (3.93–16.91)		
			Trend test *P* value, < 0.001				
		Oesophagus (squamous cell carcinoma)	Interval between tea being poured and drunk (minutes)				
			≥ 4	132	1		
			2–3	112	2.49 (1.62–3.83)		
			< 2	54	5.41 (2.63–11.14)		
			Trend test *P* value, < 0.001				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Joshi et al. (2009) Uttarakhand, India 2005–2006 Case–control	Cases: 94 endoscopy patients in one hospital; histologically confirmed Controls: 94 healthy individuals accompanying or visiting patients, matched for age, sex, and socioeconomic status Exposure assessment method: questionnaire	Oesophagus	Tea or coffee temperature Warm Hot Too hot Trend test *P* value, < 0.01	 20 50 24	 1 0.26 (0.29–1.09) 0.27 (0.25–1.28)	None	Limitations: small sample size; participation rates were not reported
Lagiou et al. (2009) 13 European centres 2002–2005 Case–control	Cases: 235, a subanalysis of the ARCAGE study (on upper aerodigestive tract cancer) Controls: 2227 from population (UK) and hospital (other centres); frequency-matched with centres by sex, age, and area Exposure assessment method: questionnaire	Oesophagus	Tea or coffee temperature Warm Hot Very hot	 NR NR NR	 1 – 0.89 (0.51–1.55)	Matching variables, BMI, height, education, alcohol consumption, smoking	Strengths: using the same protocol across study centres Limitations: number of cases by category of exposure not reported; results for "hot" tea drinking not reported

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wu et al. (2009) China, Jiangsu Province 2003–2007 Case–control	Cases: 1520 local cancer registries, confirmed by endoscopy, X-ray, or histology Controls: 3879 from population, from the same county as cases; frequency matched by age and sex Exposure assessment method: questionnaire	Oesophagus	Green tea temperature (Dafeng County)			Age, sex, education level, income 10 years before, family history of cancer, body mass index, pack-year of smoking, and alcohol drinking	Strengths: large sample size Limitations: not all cases were histologically confirmed
			Never green tea drinking	467	1		
			Normal temperature	118	1 (0.7–1.3)		
			High temperature	51	1.9 (1.2–2.9)		
		Oesophagus	Green tea temperature (Ganyu County)				
			Never green tea drinking	384	1		
			Normal temperature	244	1.3 (0.9–1.7)		
			High temperature	252	3.1 (2.2–4.3)		
Ibiebele et al. (2010) Australia 2001–2005 Case–control	Cases: 524 (238 SCC, 286 adenocarcinoma) from major treatment centres and state cancer registries; histologically confirmed Controls: 1472 from electoral rolls, by strata of age, sex, and state Exposure assessment method: questionnaire	Oesophagus (adenocarcinoma)	Tea or coffee temperature			Age, sex, alcohol intake, smoking, heartburn and reflux symptoms, BMI, education, aspirin use, and fruit, vegetable, and energy intake	Female controls were intentionally over-sampled Strengths: nationwide study; results for at least one specified histological subtype Limitations: relatively low participation among controls.
			Room temperature to lukewarm	15	1		
			Warm	28	1.56 (0.67–3.61)		
			Warm to hot	111	0.91 (0.44–1.86)		
			Hot	113	0.75 (0.37–1.54)		
			Very hot	18	0.51 (0.21–1.22)		
			Trend test *P* value, 0.02				
		Oesophagus (squamous cell carcinoma)	Tea or coffee temperature				
			Room temperature to lukewarm	8	1		
			Warm	20	1.72 (0.64–4.60)		
			Warm to hot	92	0.99 (0.42–2.32)		
			Hot	73	0.70 (0.30–1.65)		
			Very hot	35	1.28 (0.51–3.19)		
			Trend test *P* value, 0.32				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chen et al. (2011) China, Guangdong Province 2004–2010 Case–control	Cases: 150 from one hospital Controls: 300 healthy individuals visiting the hospital for routine examination, matched for sex and age Exposure assessment method: questionnaire; researchers also measured drinking temperature of tea	Oesophagus (SCC)	Tea temperature (questionnaire)			Age, sex, education level, annual income, family history of cancer, and smoking and drinking status	Strengths: results for at least one specified histological subtype Limitations: participation rates were not reported; drinking temperature measured after diagnosis in cases
			Never drinker	63	1.00		
			Warm	33	0.76 (0.36–1.32)		
			Hot	24	2.41 (1.53–4.17)		
			Very hot	30	3.69 (2.56–6.73)		
			Trend test *P* value, < 0.001				
			Tea temperature (measured, °C)				
			Never drinker	63	1.00		
			< 50	12	0.75 (0.48–1.39)		
			50–59	15	0.87 (0.54–1.55)		
			60–69	30	1.53 (0.91–2.14)		
			70–79	18	2.21 (1.57–5.53)		
			≥ 80	12	4.74 (2.67–10.51)		
			Trend test *P* value, 0.024				
Jessri et al. (2011a) Islamic Republic of Iran, Kurdistan Province NR Case–control	Cases: 50 from hospital; incident histologically confirmed oesophageal SCC diagnosed within 6 months of interview Controls: 100 patients admitted to the same hospital with acute, non-neoplastic diseases; frequency matched for sex and age Exposure assessment method: questionnaire	Oesophagus (SCC)	High temperature food/beverage consumption			Age, sex, gastro-oesophageal reflux disease, body mass index, education level, smoking status, physical activity, medication use, and total energy intake	Strengths: results for at least one specified histological subtype Limitations: participation rates and number of cases in each category of exposure not reported; small sample size
			No	NR	1.00		
			Yes	NR	3.68 (1.20–8.99)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lin et al. (2011) China, Sichuan, Guangdong Provinces 2007–2010 Case–control	Cases: 213 (175 SCC, 38 adenocarcinoma) from two hospitals Controls: 213 healthy individuals visiting the same hospital for routine examinations Exposure assessment method: questionnaire; beverage temperature included the temperature of tea, coffee, or other hot beverages	Oesophagus	Beverage temperature			Age, sex, education, smoking, alcohol drinking, body mass index, and vegetable and fruit intake	Strengths: results for at least one specified histological subtype Limitations: participation rate among controls not reported
			Luke-warm	23	1.00		
			Warm	58	1.17 (0.62–2.87)		
			Hot	92	4.13 (2.13–8.05)		
			Very hot	40	8.55 (3.67–20.90)		
			Trend test *P* value, < 0.001				
		Oesophagus (SCC)	Beverage temperature				
			Luke-warm	17	1.00		
			Warm	44	1.53 (0.82–3.24)		
			Hot	84	5.61 (2.91–11.80)		
			Very hot	30	9.12 (4.03–24.70)		
			Trend test *P* value, 0.001				
Tang et al. (2013) China, Xinjiang Uyghur Autonomous Region, 2008–2009 Case–control	Cases: 359 from four hospitals; histologically confirmed within 12 months Controls: 380 inpatient wards at the same hospitals Exposure assessment method: questionnaire	Oesophagus	Tea temperature			Age, sex, education, BMI, smoking, alcohol drinking, family history, and fruit and vegetable intake	Limitations: some cases might have been interviewed up to one year after diagnosis; no information on whether or not any cases died before the interview
			Low or mild	294	1.00		
			High temperature	65	2.86 (1.73–4.72)		
			Water temperature (drinking)				
			Low or mild	283	1.00		
			High temperature	76	2.82 (1.78–4.47)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Dar et al. (2015) Kashmir, India 2008–2012 Case–control	Cases: 703 from referral hospital; histologically confirmed Controls: 1664 from same hospital as cases or another hospital in the same city or district hospitals; individually matched for sex, age, and district Exposure assessment method: questionnaire	Oesophagus (SCC)	Salt tea temperature			Age, sex, ethnicity, residence, income, wealth score, fruit and vegetable intake, use of bidi, gutka, hookah, cigarettes, nass, and alcohol	Strengths: large sample size; results for at least one specified histological subtype
			Warm	265	1.00		
			Hot	428	1.27 (1.00–1.68)		
			Salt tea temperature			As above plus several factors related to salt tea drinking, including the amount of tea, use of milk, vessel used, roti and cereal paste consumption, adding baking soda to tea, and the way the alkaline tea was consumed	
			Warm	265	1.00		
			Hot	428	0.98 (0.73–1.30)		

[a] The Working Group noted that the description of cases and enrolment period was unclear in the translated paper
[b] The full text of this article was not available to the Working Group
BMI, body mass index; CI, confidence interval; NR, not reported; SCC, squamous cell carcinoma

a scoring system for drinking hot tea, coffee, or barley drinks defined as 0, 1, 2, or 3 for no beverages or one, two, or three types of beverage consumed burning hot, respectively. This score was associated with increased risk of cancer of the oesophagus. [The adjusted odds ratio per unit temperature score calculated by the Working Group was 2.10 (95% CI, 1.83–2.40) in men and 2.47 (95% CI, 1.87–3.26) in women ($P < 0.01$ for both sexes).]

Cook-Mozaffari et al. (1979) studied 344 cases of cancer of the oesophagus identified by the Caspian Cancer Registry in northern parts of the Islamic Republic of Iran in 1975 and 1976. The study area included Mazandaran [which later divided to Mazandaran and Golestan] and Gilan Provinces and the district of Ardabil. For each case, two population controls ($n = 688$) matched for village of residence, age, sex, and language group were selected. Approximately 20% of interviews for cancer cases were by proxy. The odds ratio (95% CI) for the association between drinking hot tea and risk of cancer of the oesophagus, versus not drinking hot tea, was 1.72 ($P < 0.01$) in men and 2.17 ($P < 0.001$) in women. The results were not adjusted for smoking and alcohol drinking, but alcohol drinking in both sexes and smoking in women were uncommon habits in that study. [The Working Group noted that it was unclear whether or not the reference groups in this study included those who did not drink the beverage of interest. However, based on the published information from related studies, drinking tea was a very common habit in this region, and adults consumed an average of 25 cups of tea per day (Ghadirian, 1987). It is therefore likely that the reference group included no or only a small number of people who did not drink tea.]

Castellsagué et al. (2000) reported results of a pooled analysis of five hospital-based case–control studies in Argentina, Brazil, Paraguay, and Uruguay (two studies). The study methods and results for mate drinking are described in Section 2.1.1. In the analysis of tea drinking, 183 cases and 333 controls were ever drinkers of tea; drinking very hot (vs cold/warm) tea was associated with an increased risk of cancer of the oesophagus (OR, 3.73; 95% CI: 1.41–9.89) in analyses adjusted for risk factors including average number of cigarettes/day, and average amount of pure ethanol/day. No association was observed between drinking very hot coffee and the risk of cancer of the oesophagus (OR, 1.01; 95% CI, 0.52–1.98). [The Working Group excluded from this review the articles published from individual studies included in the pooled analysis, including Victora et al. (1987), which was reviewed in Volume 51.]

Nayar et al. (2000) conducted a hospital-based case–control study of 150 cases and 150 controls in New Delhi, India, during 1994–1997. Controls were randomly selected from apparently healthy individuals attending with patients the same hospitals as cases. In unadjusted analysis, the researchers did not find a significant association between drinking temperature of tea and the risk of cancer of the oesophagus (OR, 1.27; 95% CI, 0.60–2.69 for "burning hot"). [Adjusted odds ratios were not reported.] The Working Group identified two earlier papers (Srivastava et al., 1995, 1997) with the possibility of overlap with the Nayar et al. (2000) study. The later, larger study (Srivastava et al., 1997) reported a crude odds ratio of 1.74 (95% CI, 1.65–2.89) for drinking "very hot" tea.

Zhang et al. (2001) reported results of a study of 214 cases of cancer of the oesophagus and 214 controls conducted in Guangdong Province, China, in 1999. In this study, those who regularly drank hot tea experienced a higher risk of cancer of the oesophagus than those who did not (OR, 2.28; 95% CI, 1.39–3.74). [The Working Group noted that the odds ratio was adjusted for several risk factors, but not for smoking or drinking alcohol. Further, it was unclear whether or not the reference groups in this study included those who did not drink the beverage of interest.]

Onuk et al. (2002) studied 44 cases of cancer of the oesophagus and 100 controls in a population-based case–control study conducted in Turkey during 1999–2000. Controls were patients with no dyspeptic symptoms and were matched to cases for age and sex. In this study, drinking hot tea (vs not drinking hot tea) was associated with an increased risk of cancer of the oesophagus (OR, 8.7; 95% CI, 2.5–30.2). [Based on the description of the study methods, the Working Group was not able to determine whether or not the results were adjusted for smoking. Further, the Working Group noted that it was unclear whether or not the reference groups in this study included those who did not drink the beverage of interest.]

Islami et al. (2009a) reported results of a population-based case–control study conducted in Golestan Province, the Islamic Republic of Iran, in 2003–2007. A total of 300 cases of squamous cell carcinoma of the oesophagus and 571 controls were recruited. Controls with no history of any cancer were selected from the same neighbourhood as that of cases and were additionally matched to cases for age and sex. Compared with drinking warm or lukewarm tea, drinking hot (OR, 2.07; 95% CI, 1.28–3.35) and very hot (OR, 8.16; 95% CI, 3.93–16.91) tea was associated with an increased risk of oesophageal squamous cell carcinoma (P for trend, < 0.001). In addition, compared with a time interval of ≥ 4 minutes between tea being poured and drunk (suggesting lower drinking temperatures of tea), shorter intervals were associated with an increased risk; the odds ratio was 2.49 (95% CI, 1.62–3.83) for an interval of 2–3 minutes and 5.41 (95% CI, 2.63–11.14) for < 2 minutes (P for trend, < 0.001). The correlation between these two variables (tea temperature and interval between tea being poured and drunk) was also examined and a weighted kappa statistic of 0.68 and Spearmans' rank correlation coefficient of 0.69 were reported. In addition to this case–control study, the actual temperature at which tea was drunk was measured for 48 582 healthy individuals in the same region. In this cross-sectional analysis, 39.0% of participants drank their tea at temperatures < 60 °C, 38.9% at 60–64 °C, and 22.0% at ≥ 65 °C. There was a moderate agreement between reported drinking temperature of tea and actual temperature measurements (weighted kappa = 0.49). [The Working Group noted that the attempt to validate drinking temperature of tea for nearly 50 000 individuals was a strength of this study. This study also used two indicators to assess tea temperature (the description of drinking temperature of tea and the duration between tea being poured and drunk), which showed a good correlation.]

Wu et al. (2009) conducted a population-based case–control study of 1520 cases of cancer of the oesophagus and 3879 controls in the counties of Dafeng and Ganyu in Jiangsu Province, China, in 2003–2007. Controls with no history of cancer were selected from the same county as cases, and were frequency-matched for age and sex. The researchers found an association between drinking high-temperature green tea and risk of cancer of the oesophagus in both Dafeng (OR, 1.9; 95% CI, 1.2–2.9) and Ganyu (OR, 3.1; 95% CI, 2.2–4.3) compared with those who did not drink tea. The odds ratio (95% CI) for the association between tea of "normal" temperature and risk of cancer of the oesophagus was 1.0 (95% CI, 0.7–1.3) in Dafeng and 1.3 (95% CI, 0.9–1.7) in Ganyu. [The Working Group noted that the reference groups in this study included those who did not drink tea. However, the risk estimates for those who drank tea of "normal" temperature was not statistically different from the reference groups, and the risk associated with drinking high-temperature tea was higher than that for drinking tea of normal temperature in both counties. Although not all cases were histologically confirmed, based on the pattern of cancers of the oesophagus in the region, most cases were likely to be squamous cell carcinoma of the oesophagus.]

Chen et al. (2011) reported results of a hospital-based case–control study conducted in Guangdong Province, China, in 2004–2010. They recruited 150 cases of squamous cell carcinoma of the oesophagus and 300 controls. Controls were matched to cases for sex and age. Compared with never drinkers of tea, those who drank hot (OR, 2.41; 95% CI, 1.53–4.17) or very hot (OR, 3.69; 95% CI, 2.56–6.73) tea had a higher risk of oesophageal squamous cell carcinoma (*P* for trend, < 0.001). The researchers also measured the actual temperature at which tea was drunk among cases and controls. The correlation coefficient between self-reported and measured drinking temperature of tea was 0.62 ($P < 0.001$). Compared with never drinkers of tea, those who drank their tea at 70–79 °C (OR, 2.21; 95% CI, 1.57–5.53) or ≥ 80 °C (OR, 4.74; 95% CI, 2.67–10.51) had a higher risk of oesophageal squamous cell carcinoma. [The Working Group noted that the reference groups in this study included those who did not drink tea. However, the risk estimates for those who drank warm tea were not statistically different from the reference groups (OR, 0.76; 95% CI, 0.36–1.32).] Those who drank hot or very hot tea were at a higher risk of cancer of the oesophagus compared with drinkers of warm tea. Similarly, the risk for those who drank their tea at temperatures of < 50 °C (OR, 0.75; 95% CI, 0.48–1.39) or 50–59 °C (OR, 0.87; 95% CI, 0.54–1.55) was not different from never drinkers of tea. Compared with these two groups who drank low-temperature tea, those who drank their tea at 70–79 °C or ≥ 80 °C were at a higher risk of cancer of the oesophagus. The measurement of drinking temperature of tea in cases was made after the development of cancer. [The Working Group noted that the correlation between measured and actual tea drinking temperatures before the development of cancer was unknown; measurements were only made after the development of cancer in cases. Patients with cancer of the oesophagus may present after dysphagia, which leads to changes in dietary habits (particularly in more advanced cases). This could cause dehydration or other changes in the mucosa, and possibly affect the temperature preference for beverages.]

Tang et al. (2013) conducted a hospital-based case–control study in Xinjiang Uyghur Autonomous Region, China, in 2008–2009. They recruited 359 cases of cancer of the oesophagus and 380 controls. Controls were recruited from inpatient wards at the same hospitals from the departments of ophthalmology, orthopaedics, respiratory disease, and physiotherapy. In this study, drinking tea at a high temperature compared with a low or mild temperature was associated with risk of cancer of the oesophagus (OR, 2.86; 95% CI, 1.73–4.72) in logistic regression analyses adjusted for age, sex, education, smoking status, alcohol drinking, family history of cancer, and daily intake of fruits and vegetables.

Dar et al. (2015) reported results of a hospital-based case–control study conducted in Kashmir, India, in 2008–2012. They recruited 703 cases of squamous cell carcinoma of the oesophagus and 1664 matched controls. In the analysis adjusted for the use of various tobacco products and alcohol and several sociodemographic characteristics, compared with drinking warm salt tea, the odds ratio for the association between drinking hot salt tea and risk of oesophageal squamous cell carcinoma was 1.27 (95% CI, 1.00–1.68). [The Working Group noted that the odds ratio is not the geometric mean of the upper and lower bounds.] This association disappeared following further adjustments for factors related to salt tea drinking habits, including the amount of tea, use of milk, the vessel used, roti and cereal paste consumption with salt tea, adding baking soda to tea, and the way in which the alkaline tea was consumed (OR, 0.98; 95% CI, 0.73–1.30).

Two studies from the USA (Brown et al., 1988 with 207 cases and 422 controls; and Yu et al. 1988 with 275 cases and 275 controls) reported finding no association between the drinking

temperature of tea and the risk of cancer of the oesophagus, but did not provide the actual results.

(b) Very hot coffee and cancer of the oesophagus

Only one case–control study and a pooled analysis of multiple case–control studies exclusively investigated the association between drinking very hot coffee and cancer of the oesophagus. Several other studies reported results for coffee and other beverages combined, for example tea and/or coffee; these studies are discussed in Section 2.2.1 (c).

In a study in Singapore, De Jong et al. (1974) reported an approximately 4-fold increase in the risk of cancer of the oesophagus associated with drinking "burning hot" coffee (compared with not drinking burning hot coffee) in models adjusted for dialect group. In multivariate models, the researchers created a scoring system for drinking hot tea, coffee, or barley drinks combined, which showed a statistically significant association with risk of cancer of the oesophagus. [For more information about study design and this composite score, see Section 2.2.1 (a).]

In a pooled analysis of five hospital-based case–control studies in South America, Castellsagué et al. (2000) did not find any association between coffee and risk of squamous cell carcinoma of the oesophagus. However, those who drank their coffee with milk at very hot temperatures were at a higher risk of oesophageal squamous cell carcinoma (OR, 2.29; 95% CI, 1.37–3.81) in logistic regression models that adjusted for age group, hospital, residency, years of education, average number of cigarettes/day, and average amount of pure ethanol/day. [For more information about this study, see Section 2.2.1 (a).]

(c) Combinations of very hot beverages and cancer of the oesophagus

One cohort study, 14 case–control studies, and one pooled analysis of five case–control studies investigated the association between drinking several types of very hot beverages combined and cancer of the oesophagus. The majority of these studies examined the effect of tea and/or coffee and sometimes included other hot liquids or foods. The studies that reported results exclusively for drinking tea or for drinking coffee are discussed in Sections 2.2.1 (a) and 2.2.1 (b), respectively.

(i) Cohort study

Tran et al. (2005) reported results of a prospective cohort study conducted in Linxian, China. A total of 29 584 individuals with no history of cancer or debilitating disease were recruited from the general population and interviewed in 1984. Participants were randomly assigned to treatment with vitamins and minerals. They received supplements for 5.25 years and were followed up until 2001. Cancer diagnoses were ascertained through local contacts and monthly visits by village health workers. Study subjects were then contacted monthly by either village health workers or interviewers. During the follow-up period, 1958 cases of squamous cell carcinoma of the oesophagus were identified. Drinking hot liquids was not associated with the risk of oesophageal squamous cell carcinoma. [The Working Group noted a possible systematic error in the reporting of some dietary factors in this study. The incidence rate for cancer of the oesophagus in Linxian was one of the highest reported rates worldwide. When this study was conducted there were health campaigns in the region highlighting possible risk factors of cancer of the oesophagus, including drinking hot tea or consuming pickled vegetables. It is possible that participants in this study had temporarily changed their dietary habits or felt uncomfortable about reporting their habits during the

campaigns. As an example, the proportion of participants in this study who reported pickled vegetable consumption was 0%, and there was no difference between cases of cancer of the oesophagus and controls in this regard. On the other hand, studies conducted in this region a few years later (after the campaigns had subsided) revealed a much higher prevalence of pickled vegetable consumption (Islami et al., 2009c); 38% of cases of cancer of the oesophagus diagnosed in 1998–1999 in a case–control study (Xibib et al., 2003) reported regular consumption of pickled vegetables 10 years before the interview (i.e. the late 1980s).]

(ii) Case–control studies

Gao et al. (1994) reported a subanalysis of a larger study of cancers of the oesophagus, pancreas, colon, and rectum conducted in Shanghai, China. For this analysis, 902 cases of cancer of the oesophagus diagnosed from 1990 to 1993 were identified from the Shanghai Cancer Registry. Using the Shanghai Resident Registry, 1552 controls frequency-matched for age and sex were randomly selected. Compared with the consumption of cold/neither cold nor hot soup/porridge, the consumption of burning hot soup/porridge [porridge is not a liquid but soup is] was associated with increased risk of cancer of the oesophagus in men (OR, 4.75; 95% CI, 3.33–6.79) and women (OR, 6.77; 95% CI, 4.09–11.20) in analyses controlling for age, education, birthplace, tea drinking, smoking, alcohol drinking, and consumption of preserved foods, vegetables, and fruit.

Garidou et al. (1996) reported results of a hospital-based case–control study conducted in Athens, Greece, in 1989–1991. The case group consisted of 43 cases of squamous cell carcinoma of the oesophagus and 56 cases of adenocarcinoma of the oesophagus; 200 controls were recruited from patients hospitalized as a result of injuries in an accident hospital. Those with alcohol-related accidents were not eligible as controls. Controls were individually matched to cases for age (± 5 years) and sex. The odds ratio for the association between the consumption of hot or very hot, compared with cold, beverages and foods and cancer risk was 1.89 (95% CI, 0.80–4.49) for oesophageal squamous cell carcinoma and 1.82 (95% CI, 0.85–3.91) for oesophageal adenocarcinoma in analyses that controlled for age, sex, birthplace, education, height, analgesics, coffee drinking, tobacco and alcohol use, and energy intake.

In a study of 208 cases of squamous cell carcinoma of the oesophagus and 399 controls in France, Launoy et al. (1997) reported an association between drinking hot calvados (an apple-based distilled alcoholic beverage) mixed with coffee and the risk of squamous cell carcinoma of the oesophagus. This study did not find a statistically significant association for cold calvados, cold spirits, and hot spirits. However, the total number of cases of cancer of the oesophagus who drank cold calvados was 13. [The Working Group noted that it would be difficult to separate the effect of temperature from that of the alcoholic beverages on the development of cancer of the oesophagus. This study also found a statistically significant inverse association between drinking whisky and the risk of oesophageal squamous cell carcinoma based on a modest number of whisky drinkers. This may suggest the presence of some other causal factors that could have distorted the association between consumption of certain types of alcoholic beverages and risk of cancer of the oesophagus in this study.]

In a pooled analysis of five hospital-based case–control studies in South America, Castellsagué et al. (2000) reported an association between drinking any combination of very hot beverages excluding and including mate, compared with never drinking the corresponding beverages at a high temperature, and cancer of the oesophagus. Odd ratios of 2.45 (95% CI, 1.72–3.49) and 2.07 (95% CI, 1.55–2.76) were reported for the groups drinking a combination

of hot beverages which excluded and included mate, respectively. [For more information about this study, see Section 2.2.1 (a)].

Cheng et al. (2000) conducted a population-based case–control study in four regions in England and Scotland in 1993–1996. The case group included 74 women with oesophageal adenocarcinoma aged < 75 years of age (< 80 years in one region), resident in the study areas at the time of their diagnosis. They recruited 74 controls that were randomly selected using the Family Health Service Authority or Health Board primary care registers. Controls were matched to cases by age (within 5 years) and general practice. There was no association between the drinking temperature of tea or coffee and the risk of adenocarcinoma of the oesophagus.

Sharp et al. (2001) reported the results of a population-based case–control study conducted in three regions in England and eastern Scotland in 1993–1996 on women. They recruited 159 women with squamous cell carcinoma of the oesophagus and 159 controls. One control was matched to each case by age and general practice. An approximately 3-fold increased risk of oesophageal squamous cell carcinoma was associated with drinking very hot or burning hot, compared with warm, tea or coffee. [The Working Group noted that results were reported by considering the reference group to be those who drunk very hot or burning hot tea or coffee. The odds ratio (95% CI) for drinking warm tea or coffee was 0.34 (95% CI, 0.13–0.88).]

Terry et al. (2001) studied 356 cases of cancer of the oesophagus (167 squamous cell carcinomas and 189 adenocarcinomas) and 815 controls selected from the entire population in Sweden. Cases were of cancer of the oesophagus identified through a nationwide cancer registry of the entire Swedish population < 80 years of age in 1995–1997. Controls were randomly selected from the Swedish population to approximate the age and sex distribution among cases. The question of tea or coffee temperature was about hot beverages consumed 20 years before interview. The researchers did not find any association between tea or coffee drinking temperature 20 years before the interview and either squamous cell carcinoma or adenocarcinoma of the oesophagus. [The Working Group noted that, in addition to those who drank cold or lukewarm tea or coffee, the reference group in this study also included those who did not drink tea or coffee.]

Hung et al. (2004) reported results of a hospital-based case–control study conducted in Taiwan, China, in 1996–2002 on men. They recruited 365 men with squamous cell carcinoma of the oesophagus and 532 controls. Controls were individually matched to cases for age and hospitalization date. Those who consumed hot drinks or soup three times or more per day at the age of 20–40 years were at a higher risk of oesophageal squamous cell carcinoma (OR, 1.8; 95% CI, 1.1–3.0) than those who did not. There was no such association for patients of age ≥ 40 years in this study (OR, 1.3; 95% CI, 0.8–2.1). [The Working Group noted that data from this study may be included in a later study by Chen et al. (2009). Further, the reference group included those who consumed hot drinks or soups fewer than three times per day and might have included those who did not drink hot liquids.]

Yokoyama et al. (2006) reported results of a hospital-based case–control study conducted among women in Japan in 2000–2004. Cases were 52 women with squamous cell carcinoma of the oesophagus treated at four hospitals (in Chiba, Kanagawa, Osaka, and Tokyo). Controls consisted of 412 cancer-free women who visited two clinics in Tokyo for annual health check-ups. The researchers categorized preference for hot foods or drinks to one of five groups. Compared with the group "dislike very much", the category of "like very much" was associated with a higher risk of oesophageal squamous cell carcinoma (OR, 3.43; 95% CI, 0.39–30.46; adjusted for age only). The reference category, however,

consisted of only one case subject. [The Working Group combined the three categories of "dislike very much", "dislike somewhat", and "neither like or dislike" using frequencies of cases and controls provided in the article, and considered this combined group as the reference group. Compared with this group, the category of "like very much" was associated with oesophageal squamous cell carcinoma (unadjusted OR, 3.24; 95% CI, 1.27–7.68).]

Joshi et al. (2009) reported results of a hospital-based case–control study conducted in Uttarakhand, India, in 2005–2006. They recruited 94 cases of cancer of the oesophagus and 94 controls. Cases were selected from those who underwent upper gastrointestinal endoscopy in one hospital. Controls were healthy individuals who accompanied the cases or other patients who attended the hospital, matched to cases for age, sex, and socioeconomic status. Compared with drinking warm tea or coffee, drinking hot or "too hot" tea or coffee was not associated with an increased risk of cancer of the oesophagus. There was evidence of an inverse exposure–response trend of risk of cancer of the oesophagus with tea or coffee temperature ($P < 0.01$).

Lagiou et al. (2009) reported results of the Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) study, a multicentre case–control study on cancers of the upper aerodigestive tract in 13 centres in nine countries across Europe (Croatia, Czech Republic, Germany, Greece, Ireland, Italy, Norway, Spain, and the United Kingdom). For this analysis, 235 cases of cancer of the oesophagus (from 10 centres) and 2227 controls were included. Controls were frequency-matched to cases for sex, age (5-year groups), and referral (or residence) area within each study centre. There was no association between drinking temperature of tea or coffee and risk of cancer of the oesophagus.

Ibiebele et al. (2010) reported results of a nationwide population-based case–control study conducted in Australia in 2001–2005. They recruited 524 cases of cancer of the oesophagus and 1472 controls. Cases included 524 patients aged 18–79 years with cancer of the oesophagus (238 squamous cell carcinomas and 286 adenocarcinomas) identified through major treatment centres throughout Australia or by state-based cancer registries. Controls were randomly selected from the Australian electoral roll and sampled from within strata of sex and age and state of residence. The researchers did not find an association between tea or coffee temperature and either squamous cell carcinoma or adenocarcinoma of the oesophagus. The trend analysis, however, suggested a trend for an inverse association between tea or coffee temperature and oesophageal adenocarcinoma risk (P for trend = 0.02).

Jessri et al. (2011a) conducted a hospital-based case–control study of 50 cases of squamous cell carcinoma of the oesophagus and 100 controls in the Islamic Republic of Iran. Controls were individuals admitted to the same hospital as cases for a wide spectrum of acute non-neoplastic diseases that were not related to smoking, alcohol abuse, or long-term modification of the diet. The consumption of high-temperature foods or beverages was associated with an increased risk of oesophageal squamous cell carcinoma (OR, 3.68; 95% CI, 1.20–8.99). [Based on another publication from this study, which provided the frequency distribution but not odds ratio for food or beverage temperature, the Working Group noted that the reference group included those who consumed warm/cold foods or beverages (Jessri et al., 2011b).]

Lin et al. (2011) reported results of a hospital-based case–control conducted in Sichuan and Guangdong Provinces, China, in 2007–2010. They recruited 213 cases of cancer of the oesophagus (175 squamous cell carcinoma) and 213 controls selected from healthy individuals visiting the same hospital during the same period as cases for routine physical examination. Compared

with drinking lukewarm beverages, drinking hot (OR, 4.13; 95% CI, 2.13–8.05) and very hot (OR, 8.55; 95% CI, 3.67–20.90) beverages was associated with an increased risk of cancer of the oesophagus (*P* for trend, < 0.001). The respective odds ratios for oesophageal squamous cell carcinoma were 5.61 (95% CI, 2.91–11.8) and 9.12 (95% CI, 4.03–24.7) (*P* for trend, < 0.001).

Tang et al. (2013) conducted a hospital-based case–control study in Xinjiang Uyghur Autonomous Region, China. A total of 359 newly diagnosed cases of cancer of the oesophagus (in 2008–2009) were identified by retrospective reviewing of medical records and pathology in four hospitals. A total of 380 controls were recruited from inpatient wards at the same hospitals Drinking water of high temperature (OR, 2.82; 95% CI, 1.78–4.47) and tea of high temperature (OR, 2.86; 95% CI, 1.73–4.72), compared with water or tea of low or mild temperature, was associated with increased risk of cancer of the oesophagus.

(d) Systematic reviews and meta-analyses

At least three systematic reviews have examined the association between drinking hot beverages and risk of cancer of the oesophagus (Islami et al., 2009c; Andrici & Eslick, 2015; Chen et al., 2015b). Two of these reviews estimated a pooled odds ratio for the association. Andrici & Eslick (2015) reported an overall odds ratio of 2.28 (95% CI, 1.62–3.22) for the association between the consumption of hot beverages (other than mate) or food and risk of squamous cell carcinoma risk of the oesophagus. The odds ratio for 11 studies on all hot beverages (including mate) and food, with results adjusted for smoking and alcohol drinking, was 2.39 (95% CI, 1.71–3.22). [A meta-OR of adjusted results excluding mate was not reported.] There was no statistically significant association between hot beverage or food consumption and oesophageal adenocarcinoma based on the results of four studies (OR, 0.78; 95% CI, 0.45–1.35). Chen et al. (2015) reported an odds ratio of 1.82 (95% CI, 1.53–2.17) for the association between hot beverage and food consumption (including mate) and risk of cancer of the oesophagus (39 studies), 1.60 (95% CI, 1.29–2.00) for squamous cell carcinoma of the oesophagus (26 studies), and 0.79 (95% CI, 0.53–1.16) for adenocarcinoma of the oesophagus (4 studies). The corresponding odds ratio was 2.06 (95% CI, 1.62–2.61) in Asia (28 studies), 1.52 (95% CI, 1.25–1.85) in South America (13 studies), and 0.95 (95% CI, 0.68–1.34) in European populations (5 studies). The pooled odds ratios were comparable for hot tea, mate, and other beverages (ranging from 1.72 to 1.88). There was high heterogeneity in most analyses performed in these two meta-analyses. [The Working Group noted that the systematic reviews are informative for synthesis of the information but, given the high heterogeneity in the meta-analyses, regional differences in incidence, and the subjective nature of the exposure (preference for hot beverages), meta odds ratios for the association between hot beverages and cancer of the oesophagus and should be interpreted with caution. The Working Group also noted the inclusion of several overlapping studies in the meta-analysis of Chen et al. (2015), notably original reports from studies included in the pooled analysis of Castellsagué et al. (2000), as well as the pooled analysis.]

2.2.2 Other cancers

See Table 2.2.2 (web only; available at: http://publications.iarc.fr/566).

(a) Cancer of the upper aerodigestive tract

Martinez (1969) studied 179 cases of cancer of the oesophagus, 153 cases of cancer of the mouth, and 68 cases of cancer of the pharynx, all histologically confirmed cases of squamous cell carcinoma reported to the Puerto Rico Cancer Registry in 1966. As controls, one non-cancer patient from the same hospital and two

individuals from the community were matched to each case for age and sex. The results were shown for cancer of the mouth, pharynx, and oesophagus combined. There was a significant association between drinking hot coffee [OR, 2.14; 95% CI, 1.36–3.35] or hot coffee with milk [OR, 1.47; 95% CI, 1.01–2.12], versus drinking cold or warm coffee, and cancer at these three sites. The results were not adjusted for major causes of upper aerodigestive tract cancers, notably smoking.

Franco et al. (1989) reported results of a study of the association between drinking hot coffee and cancer of the oral cavity (tongue, gum, floor of the mouth, and other parts of the oral cavity) conducted in Brazil in 1986–1988. Cases ($n = 232$) were selected from patients referred to three head and neck surgery services in three cities. Two control subjects for each case were selected from patients in the same hospital as cases or from neighbouring general hospitals. Controls were matched to cases for sex, age, and trimester of hospital admission. The researchers did not show the results, but they reported that they did not find any association between drinking "burning hot" coffee, compared with drinking coffee at lower temperatures, and the risk of cancer of the oral cavity.

Gridley et al. (1990) conducted a population-based case–control study of cancer of the oral cavity and pharynx among African Americans in the USA. Cases (n = 190) were histologically confirmed incident cases of cancer of the tongue, pharynx, and other oral cancers excluding cancers of the lip, salivary gland, or nasopharynx, and were identified from the population-based cancer registries of New Jersey, Atlanta, Los Angeles, and counties of Santa Clara and San Mateo in California. A total of 201 controls matched for sex and age were selected using random-digit dialling and Health Care Financing Administration rosters. Proxy interviews were conducted for 29% of cases, but only and 1% of controls. The data were not reported, but the researchers stated that there was no association between drinking hot beverages and risk of cancer of the oral cavity or pharynx.

In the the ARCAGE study, described previously (Lagiou et al., 2009), there were 2304 cases with cancer of the oral cavity, pharynx (excluding nasopharynx), larynx, or oesophagus, and 2227 controls. Compared with drinking warm tea or coffee, the researchers found an inverse association between drinking hot (OR, 0.78; 95% CI, 0.65–0.92) or very hot (OR, 0.67; 95% CI, 0.52–0.86) tea or coffee and the risk of cancers of the upper aerodigestive tract (P for trend < 0.001). [For more details of this study, see Section 2.2.1 (c).]

Chen et al. (2015) conducted a population-based case–control study of 203 cases with cancer of the oral cavity and 572 controls in Fujian Province, China, in 2011–2015. All cases and controls were non-smokers and non-drinkers of alcohol. This study reported an inverse association between drinking tea at moderate temperatures (OR, 0.55; 95% CI, 0.31–0.98; based on 17 cases) or high temperatures (OR, 0.50; 95% CI, 0.28–0.88; based on 18 cases) and the risk of cancer of the oral cavity, compared with never drinkers of tea. [The Working Group noted that the inverse associations were observed when never drinkers of tea were the reference group. There was no difference between the reported risk associated with drinking tea at moderate temperatures and drinking tea at high temperatures, and 95% confidence intervals for these two risk estimates were fully overlapping.]

(b) Cancer of the stomach

Pourfarzi et al. (2009) conducted a population-based case–control study of cancer of the stomach in Ardabil Province, the Islamic Republic of Iran, in 2004–2005. Cases (n = 217) were identified from the Ardabil Cancer Registry, which listed cancer surveillance data from doctors and pathology services making a cancer diagnosis in Ardabil, as well as from an active surveillance for cancer of the stomach conducted

by the Cancer Registry through all hospitals and clinics in the province. A total of 394 controls were randomly selected from the community using a sampling frame created for the annual household survey by the health department. Drinking hot tea versus non-hot tea was associated with an increased risk of cancer of the stomach (OR, 2.85; 95% CI, 1.65–4.91) in models adjusted for gender, age group, education, family history of gastric cancer, *Helicobacter pylori*, and dietary factors.

Deandrea et al. (2010) conducted a hospital-based case–control study of the association between drinking green tea and cancer of the stomach in Heilongjiang Province, China, in 1987–1989. Cases ($n = 266$) were newly diagnosed cancer of the stomach cases admitted to six hospitals. Controls ($n = 533$) were patients admitted for non-neoplastic and non-gastric diseases to surgical departments at the same hospitals. The researchers reported results based on exposure at three time points, which were usual green tea drinking temperatures in 1961 (around the time of the Great Chinese Famine), 1966 (the beginning of the cultural revolution), and the 1980s (close to the time of interview). However, the results for 1961 and 1966 were based on only 10 and 20 drinkers of green tea, respectively. The researchers did not find any statistically significant evidence of an association between the risk of cancer of the stomach and drinking hot green tea in any quantity. [The Working Group noted that the reference group in this study consisted of those who did not drink green tea. Compared with not drinking green tea, the pooled odds ratio for drinking either < 750 g/year or ≥ 750 g/year lukewarm green tea calculated by the Working Group was 0.31 (95% CI, 0.16–0.60). This risk estimate suggests that drinking hot green tea was associated with an increased risk of cancer of the oesophagus when compared with drinking lukewarm tea in this study. However, the risk estimate for lukewarm tea was based on only 11 cancer cases in the exposed group.]

Mao et al. (2011) reported results of a hospital-based case–control study of the association between drinking green tea and cancer of the stomach conducted in Yunnan Province, China, in 2010–2011. They recruited 200 cases from two hospitals and 200 age- and sex-matched controls who were healthy individuals visiting a different hospital for routine physical examination. Compared with never drinkers of green tea, drinkers of hot (OR, 1.82; 95% CI, 1.03–3.52) or very hot (OR, 3.07; 95% CI, 1.78–7.36) green tea experienced a higher risk of cancer of the stomach. No statistically significant association between risk of cancer of the stomach and tea temperature combined with either smoking ($P = 0.24$) or drinking alcohol ($P = 0.37$) was found. [The Working Group noted that the reference group in this analysis consisted of those who did not drink tea. However, the reported risk associated with drinking cool (OR, 0.85; 95% CI, 0.54–1.72) or warm (OR, 0.81; 95% CI, 0.58–0.97) green tea was not different from the reference group. Based on the reported odds ratios and 95% confidence intervals, this study indicates an association between drinking hot or very hot green tea, compared with drinking green tea at lower temperatures, and cancer of the stomach.]

Wang et al. (2015) conducted a hospital-based case–control study of the association between drinking temperature of green tea and risk of cancer of the stomach in Shenyang and Zhengzhou, China, in 2005–2010. They recruited 160 cases from two hospitals and 320 randomly selected controls matched for sex from outpatients without a diagnosis of cancer at the same hospitals. Compared with drinking lukewarm or cool green tea, drinking warm (OR, 1.64; 95% CI, 1.16–2.41) or hot (OR, 3.13; 95% CI, 1.85–5.11) green tea was associated with an increased risk of cancer of the stomach. [The researchers reported adjusted results, but the covariates were unclear to the Working Group.] The analysis was repeated among men and

women separately to examine the potential confounding effects of smoking [which in China is generally much less common in women], and found similar results [data were not shown].

(c) Cancer of the skin

Hakim et al. (2000) reported results of a population-based case–control study conducted in Arizona, USA. Participants in the baseline study were recruited in 1993–1996, and were contacted again by telephone in 1998 to complete a tea consumption questionnaire. For this analysis, 234 cases of squamous cell carcinoma of the skin were randomly selected from people identified via the Southeastern Arizona Skin Cancer Registry as a first occurrence of squamous cell carcinoma of the skin; 216 controls were selected using the method of random-digit dialling. Compared with not drinking tea, there was no association between drinking warm (OR, 1.51; 95% CI, 0.37–6.12) or hot (OR, 0.76; 95% CI, 0.56–1.01) tea and squamous cell carcinoma of the skin in this study. [The Working Group noted that the reference group in this study included non-drinkers of tea. However, there was no difference between the risk associated with drinking warm tea and drinking hot tea, with fully overlapping 95% confidence intervals for the risk estimates.]

(d) Cancer at multiple sites combined

One of the Islamic Republic of Iran studies on cancer of the oesophagus (Cook-Mozaffari et al., 1979) also studied a second group of 181 patients with cancers of the lung, stomach, breast, large bowel, larynx, and pharynx (approximately 50% with cancer of the stomach) with 2 matched neighbourhood controls per case. Approximately 20% of interviews for cancer cases were by proxy. In this study, drinking hot tea was associated with a higher risk of cancers other than cancer of the oesophagus in men (OR, 3.23; $P < 0.001$), but not in women (OR, 0.86; $P > 0.05$). The results were not adjusted for smoking. The researchers stated that the increased risk mainly reflected the association with cancer of the stomach, but they did not report the results for cancer of the stomach (or any cancer other than that of the oesophagus) separately.

3. Cancer in Experimental Animals

There were no data in experimental animals regarding the carcinogenicity of mate in the previous *IARC Monographs* evaluation (Volume 51; IARC, 1991).

See Table 3.1.

3.1 Mate

In the study by Silva et al. (2009), three groups of male Wistar rats (age, 6 weeks) were given *N*-nitrosodiethylamine (NDEA) at a dose of 80 mg/kg body weight (bw) intraperitoneally in saline once per week for 8 weeks, with (two groups of 20 rats) or without (5 rats) concomitant treatment with 1 mL of water at 65 °C instilled in the oesophagus by a metal probe twice per week for 8 weeks. The rats were given a single source of drinking-water with or without mate (2% w/v; 20 g of dried and minced leaves of *I. paraguariensis* was added to 1 L of hot water at 70 °C for 20 minutes, then filtered and allowed to cool down to room temperature), for 8 weeks. Two groups of five rats served as additional controls and were given intraperitoneal injections of 1 mL of saline (vehicle) once per week and a single source of drinking-water at 25 °C, with or without mate (2% w/v), twice per week for 8 consecutive weeks. The rats were killed 20 weeks after the start of treatment. There was a body-weight loss in rats treated with NDEA either alone (266.8 ± 27.8 g) or together with hot water (260.8 ± 29.5 g) ($P < 0.001$) when compared with rats treated with NDEA, hot water, and mate (296.8 ± 32.8 g). Five rats were found dead during

Table 3.1 Studies of carcinogenity in experimental animals exposed to mate or very hot water

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dosing regimum Animals per group at start	Results for each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Co-carcinogenicity Rat, Wistar (M) Age, 6 wk 20 wk Silva et al. (2009)	Mate given as drinking fluid in distilled water (2% w/v) NDEA (80 mg/kg bw) intraperitoneally 1×/ wk for 8 wk + water at 65 °C by gavage (1 mL, 2×/ wk for 8 wk) + water (control) or mate for 8 wk 20 mice/group	*Liver* Incidence of adenoma: 8/12, 1/13 *Oesophagus* Incidence of papilloma: 7/12, 2/13	$P < 0.001$ (reduction) $P < 0.05$ (reduction)	Survival, 12/20, 13/20
Co-carcinogenicity Mouse, BALB/c (F) Age, 2 mo Up to 32 wk Rapozo et al., (2016)	Oesophageal installation of hot water (70 °C) NDEA (> 99%) at 10 ppm in the drinking-water with or without (control) 0.3 mL hot water, 3×/wk 10, 11 mice/group	*Oesophagus* Squamous cell papilloma or carcinoma (combined), at 8 wk Tumour incidence: 0/10, 1/11 Total tumours: 0, 1	 NS NS	Principal strengths: dose–response design experiment; hot water at 50 °C and 60 °C also tested Treatment with 10 ppm NDEA alone induced focal hyperplasia in only 1 mouse out of 7 at 16 wk of treatment. Treatment with water at 70 °C and 10 ppm NDEA (combined) produced oesophageal lesions at all time intervals: Hyperplasia: 3/5 at 2 wk; 3/5 at 4 wk; 5/11 at 8 wk; and 1/8 at 16 wk High-grade dysplasia – 1/11 at 8 wk; focal hyperplasia – 1/5 at 4 wk, 3/11 at 8 wk; and 5/8 at 16 wk
Initiation–promotion (tested as promoter) Rat, F344 M Age, 12 wk 20 wk Li et al. (2003)	Gavage (hot water) Hot water (55 °C or 65 °C) at 1 mL/kg bw + NMBzA (purity, 99%) at 1 mg/kg bw subcutaneously 0.9% NaCl 65 °C + NMBzA, 55 °C + NMBzA, NMBzA (control) 5 × /wk for 5 wk then 1 × /wk for 10 wk 11, 9, 9 mice/group	*Oesophagus* Squamous cell papilloma or carcinoma (combined) Tumour multiplicity: 8.0 ± 2.1*[a], 5.7 ± 2.1, 5.5 ± 1.5[b] Total tumours: 89, NR, 47	*$P < 0.05$; [a] 18 papillomas, 44 papillomas with atypia, and 27 carcinomas (increase in the number of carcinomas, $P < 0.05$); [b] 19 papillomas, 20 papillomas with atypia, and 8 carcinomas	Principal strengths: good histopathological analysis, dose–response design of experiment, adequate number of tumours produced Principal limitations: small number of rats, loss of weight, and animal death caused by hot water Survival, 9/11, 9/9, 9/9

bw, body weight; mo, month; NA, not applicable; NDEA, *N*-nitrosodiethylamine; NMBzA, *N*-nitrosomethylbenzylamine; NR, not reported; NS, not significant; wk, week

the experiment: three from the group treated with NDEA and hot water; and two from the group treated with NDEA, hot water, plus mate. There was no induction of malignant tumours of the oesophagus, but treatment with mate reduced the incidence of oesophageal neoplastic lesions when compared with treatment with NDEA plus water at 65 °C. There were 2 out of 13 rats with papilloma of the oesophagus in the group treated with mate plus hot water and NDEA, versus 7 out of 12 rats in the group treated with hot water and NDEA ($P < 0.05$, decrease). There was also a significant ($P < 0.001$, decrease) reduction in the incidence of adenoma of the liver (1 out of 13 rats in the group treated with NDEA, hot water, and mate, vs 8 out of 12 rats in the group treated with NDEA and hot water). [The Working Group noted that there were no tumour data on rats given NDEA only.]

3.2 Very hot water

3.2.1 Mouse

In the study by Rapozo et al. (2016), female BALB/c mice (age, 2 months) were given drinking-water containing NDEA at a concentration of 10 ppm and/or water at different temperatures (25, 50, 60, or 70 °C, instilled by a metal straw into the oesophagus) three times per week for up to 32 weeks. Cohorts of [presumably up to 11] mice were killed periodically between 24 hours and 32 weeks, and a histopathological examination was conducted for diagnosis of oesophageal preneoplastic lesions. There was approximately 15% mortality in the cohorts that were given water at 70 °C during the first 2 weeks of treatment. There was body-weight loss in the group of mice treated with 70 °C hot water (mean body-weight loss, from 19 g to 16 g) during the second week of treatment, but the mice recovered at the third week (mean body weight, 22 g). The study clearly showed a coagulation necrosis of the oesophagus produced by hot water at 70 °C, and that this damage healed when NDEA was not given together with water at 70 °C. Treatment of mice with hot water at either 50 °C or 60 °C did not produce weight loss, death, or coagulation necrosis of the oesophagus. Mice treated with water at 70 °C for up to 32 weeks did not develop hyperplasia, dysplasia, or tumours of the oesophagus. Treatment with NDEA at 10 ppm alone induced focal hyperplasia of the oesophagus in only 1 mouse out of 7 at 16 weeks of treatment. Treatment with water at 70 °C and NDEA at 10 ppm (combined) produced oesophageal lesions – including preneoplastic lesions – at all time intervals: hyperplasia – 3 out of 5 at 2 weeks, 3 out of 5 at 4 weeks, 5 out of 11 at 8 weeks, and 1 out of 8 at 16 weeks; high-grade dysplasia – 1 out of 11 at 8 weeks; focal hyperplasia – 1 out of 5 at 4 weeks, 3 out of 11 at 8 weeks; and 5 out of 8 at 16 weeks. In addition, 1 out of 11 mice treated with water at 70 °C and 10 ppm NDEA (combined) had a squamous cell papilloma at 8 weeks. Mice that were given NDEA plus 70 °C water treatment had an almost nine times higher chance of developing oesophageal lesions when compared with mice given NDEA only ($P = 0.0042$). [Regarding data from Rapozo et al. (2016), the Working Group observed that several lesions originally presented as preneoplastic lesions should be considered as squamous cell papillomas.]

3.2.2 Rat

In a study by Yioris et al. (1984), four groups of 30 male and 30 female Wistar rats (age, 3 months) were given either 65 °C water (3 mL, instilled with a metal probe 2 cm above the cardia, twice per week for a total of 50 treatments) or *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG, 5.0 mg/kg bw by gavage five times per week for a total dose of 900 mg/kg bw), or the combined treatment (in this case the total dose of MNNG was 700 mg/kg bw because of the interruption of treatment) for 37 weeks. Treatment with hot water produced a considerable deterioration of

the rats, leading to a brief interruption of treatment at 4 and 20 weeks [additional details on the interruption not provided]. Rats were allowed to live their lifespan. There was a reduction in mean survival among rats treated with hot water (420 days) and with MNNG (370 days), a reduction that was even more pronounced with the combined treatment (280 days) when compared with controls (580 days). Water at 65 °C alone or MNNG alone did not produce tumours of the oesophagus, whereas the combined treatment produced malignant polymorphocellular sarcomas of the oesophagus in 4 out of 30 rats [not statistically significant] at the location where hot water was instilled. [The Working Group noted that different groups were not given the same total dose of MNNG, and that the 3 mL volume of hot water instilled was very large for the oesophagus of the rat. This study was therefore considered inadequate for evaluation.]

Groups of male F344 rats (age, 12 weeks) were given *N*-nitrosomethylbenzylamine (NMBzA) subcutaneously at a dose of 1 mg/kg bw, or hot water (1 mL/kg bw at 55 °C or 65 °C by oesophageal intubation), or a combination of these (Li et al. (2003)). Groups sizes were 5 rats (groups receiving only saline or only hot water at either temperature), 9 rats (groups receiving NMBzA alone or with hot water at 55 °C), or 11 rats (group receiving NMBzA and hot water at 65 °C). Both agents were given five times per week for 5 weeks and then once per week for 10 weeks. The experiment was concluded at 20 weeks due to the rapid progression of tumours caused by NMBzA plus hot water. Rats that received NMBzA and hot water at 65 °C presented a statistically significant ($P < 0.05$) reduction in their body weight as compared with rats in the control group. None of the 5 rats that received only saline or only hot water at either temperature developed tumours of the oesophagus. There was a statistically significant increase in the mean number of squamous cell papillomas or carcinomas (combined) per rat (11 rats) that received NMBzA and 65 °C hot water (8.0 ± 2.1, $P < 0.05$) compared with those treated with NMBzA alone (9 rats) (5.5 ± 1.5). Treatment with NMBzA and 55 °C hot water (9 rats) did not produce an increase in tumour multiplicity (5.7 ± 2.1) when compared with NMBzA alone. Hot water at 65 °C increased NMBzA-induced carcinogenesis: rats that received NMBzA developed 47 tumours (19 squamous cell papillomas, 20 squamous cell papillomas with atypia, and 8 squamous cell carcinomas), whereas rats that received the combined treatment of NMBzA and hot water at 65 °C developed 89 tumours (18 squamous cell papillomas, 44 squamous cell papillomas with atypia, and 27 squamous cell carcinomas; increase in the number of carcinomas, $P < 0.05$). [The Working Group considered that the study was well designed and well conducted, with an exposure–response relationship regarding hot water temperature. There was, however, a small number of rats per group, particularly in the group treated with hot water only.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion of mate

4.1.1 Absorption and distribution

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

The only study available evaluated 5-caffeoylquinic acid (5-CQA), caffeic acid (CA), and caffeine absorption and distribution in male Wistar rats given single or multiple (during a 30-day period) oral dose(s) of mate infusion extract, either hydrolysed or unhydrolysed

(Rivelli et al., 2011). [Hydrolysis was performed using chlorogenate esterase in a process that is not involved in traditional mate preparation.] The extract contained 7.93% 5-CQA, 1.48% CA, and 162 ± 5 µmol equiv quercetin/g. Maximum plasma concentrations (C_{max}) of 5-CQA and CA were achieved 10 and 20 minutes after extracts were administered, respectively. Hydrolysis increased the CA plasma concentration, whereas caffeine reached a higher C_{max} after ingestion of nonhydrolysed extract. 5-CQA was only evaluated after the unhydrolysed extract was administered, and was below the detection limit.

Distribution of 5-CQA, CA, and caffeine was assessed at the time of highest plasma concentration by high-pressure liquid chromatography analysis of liver, brain, and skin samples. In liver, only CA was found in rats treated with hydrolysed extract. None of the compounds was detected in brain or skin.

4.1.2 Metabolism

(a) Humans

No data were available to the Working Group in exposed humans.

However, two studies examined the effect of the mate plant on human metabolic enzyme activities in vitro. In human placental microsomes, ursolic acid was an efficient and dose-dependent aromatase inhibitor, with the half-maximal inhibitory concentration (IC_{50}) of 32 µM (Gnoatto et al., 2008). Martins et al. (2010) reported dose-dependent inhibition of human pancreatic lipase at 37 °C, with the maximal inhibition observed at mate tea concentration of 3.0 mg/mL, i.e. 9 mg of tea per gram of substrate (79 ± 1.3% inhibition). The IC_{50} value was estimated to be 1.5 mg/L or 4.5 mg of mate tea per gram of substrate.

(b) Experimental systems

No data in vivo were available to the Working Group.

One study in vitro explored modulation of pancreatic lipase (Martins et al., 2010), reporting dose-dependent, competitive inhibition with the maximal inhibition observed at a mate-preparation concentration of 3.0 mg/mL, corresponding to 9 mg of preparation per gram of substrate (83 ± 2.1% inhibition). The IC_{50} was determined to be 1.5 mg/L or 4.5 mg of mate preparation per gram of substrate.

4.1.3 Excretion

No data were available to the Working Group.

4.2 Mechanisms of carcinogenesis

For the experiments discussed below, the temperature of mate at which the experiments were conducted was not specified unless otherwise indicated.

4.2.1 Genetic and related effects

(a) Mate

(i) Humans

See Tables 4.1 and 4.2.

Only two studies in exposed humans were available, and neither evaluated the recommended number of cells (2000) according to a recently published micronucleus protocol (Thomas et al., 2009). A study of 145 mate drinkers and 99 non-drinkers reported induction of micronuclei (MN) in oesophageal cells by mate (Dietz et al., 2000). In the overall group of mate consumers, no effect was observed in comparison to the controls, and neither smoking nor alcohol influenced the MN levels. No increase in MN frequencies was observed in a small intervention trial without controls (Bortoluzzi et al., 2014), in which 10 volunteers consumed mate at 1 L/day over a week (4 drinks/day for 7 days). Buccal cells were collected 14–16 days after the intervention. [The Working Group noted that

Table 4.1 Genetic and related effects of drinking mate in humans

Cell type	End-point	Test	Description of exposure and controls	Result/ significance	Comments	Reference
Oesophageal cells	Chromosomal damage	Micronucleus formation	Healthy subjects (145 consumers and 99 non-consumers)	(–)	Only 500 cells were evaluated; no increase of micronuclei due to alcohol consumption or smoking	Dietz et al. (2000)
Buccal cells	Chromosomal damage	Micronucleus formation	Intervention trial with 10 healthy subjects who consumed 4 drinks/ day for 7 days	(–)	Only 1000 cells were evaluated	Bortoluzzi et al. (2014)

(–), negative in a study of limited quality

cells were stained with Giemsa, which is not suitable for this test (Nersesyan et al., 2006).]

In cells collected from patients with squamous cell carcinoma of the oesophagus from an area in Brazil of high risk where mate is consumed at high temperatures, Pütz et al. (2002) reported increased levels of *TP53* gene mutations. Information concerning demographic data and lifestyle factors, including alcohol, mate consumption, and smoking, were collected with questionnaires. The type of alterations found differed from that detected in cancer of the oesophagus in other geographic areas, i.e. a relatively high number of transition mutations was reported (G > A, C > T, and A > G). [The Working Group noted that this conclusion was based on comparisons with results from other studies.]

In an in vitro study of human lymphocytes, Fonseca et al. (2000) reported a significant increase of chromosomal aberrations after treatment with mate at concentrations of 50–750 µg/mL, while higher concentrations were not clastogenic. In the presence of metabolic activation mix (S9), only the highest test concentration (750 µg/mL) was clastogenic while lower amounts (100, 250, and 500 µg/mL) were ineffective.

Two groups reported on the formation of MN with the cytokinesis-block method in cultured human lymphocytes. While Alves et al. (2008) found no evidence for mutagenic and cytotoxic activities, a clear positive result was reported by Wnuk et al. (2009). The latter authors also used fluorescence in situ hybridization (FISH) probes and found that aneugenic effects contribute to the formation of MN.

(ii) Experimental systems

See Tables 4.3 and 4.4.

Two studies using the comet assay in laboratory rodents yielded negative results. The first examined genotoxic effects in rats of nitrosamines in combination with high temperatures (Silva et al., 2009). Mate (2.0% in drinking-water) did not induce DNA strand breaks in leukocytes, whereas protective effects of mate (given over 8 weeks) were found in combination experiments with diethylnitrosamine (Silva et al., 2009). In mice, mate solutions (60 days) did not induce strand breaks in cells from the liver, kidneys, and bladder (Miranda et al., 2008). At the highest dose (2.0 g/kg), a small but significant reduction of comet formation was observed (Miranda et al., 2008). In parallel experiments, a protective effect of mate ingestion on DNA strand breaks was seen

Table 4.2 Genetic and related effects of mate in human lymphocytes in vitro

End-point	Test	Results[a]		Dose (LED or HID)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Chromosomal damage	Chromosomal aberrations	+	+	50 µg/mL without S9; 750 µg/mL S9		Fonseca et al. (2000)
Chromosomal damage	Micronucleus	–	NT	1400 µg/mL		Alves et al. (2008)
Chromosomal damage	Micronucleus	+	NT	10.0 µg/mL	100 and 1000 µg/mL were ineffective	Wnuk et al. (2009)

+, positive; –, negative; HID, highest ineffective dose; LED, lowest effective dose; NT, not tested; S9, 9000 × *g* supernatant from rat liver

when isolated liver cells were exposed to reactive oxygen species (ROS) (H_2O_2) (see also Section 4.2.2). No increase in chromosomal aberrations in bone marrow cells was seen in male and female Wistar rats treated once intragastrically with mate (1.0 and 2.0 g/kg), or with the same doses divided over 4 consecutive days Fonseca et al. (2000).

In non-mammalian systems, Fonseca et al. (2000) mate was positive in *Salmonella* strains TA100 and TA102 (but not in TA97 and TA98 strains) and in assays for phage induction with *E. coli* (strains WP2sλ and RJF013). In *E. coli*, results were negative when exogenous activation mix (S9) was added. [The Working Group noted that no positive controls were used in the experiments and no standard deviations (SDs) are shown in the results.] In *Saccharomyces cerevisiae* (Candreva et al., 1993), hot (but not cold) mate was mutagenic.

(b) Hot beverages

(i) Humans

A Canadian study (61 patients) reported an impact of hot beverage consumption (recorded with questionnaires) on the levels of *TP53* mutations in primary carcinomas of the oesophagus (Casson et al., 1998). The number of mutations increased as a function of the number of hot drinks consumed and with beverage temperature.

In a study of *TP53* mutation patterns in samples of squamous cell carcinomas of the oesophagus obtained from subjects in Golestan Province in the Islamic Republic of Iran, almost all samples were positive for mutations (Abedi-Ardekani et al., 2011). A total of 120 *TP53* mutations were detected in 107 out of 119 cases (89.9%), and a significant concordance in patterns of *TP53* mutations (G:C to A:T mutations at CpG sites) was found with respect to the self-reported temperature of tea consumption (measured in terms of the number of minutes the subject usually waited after pouring boiling water onto tea before drinking it).

[The Working Group noted the difficulty in assessing the relevance of these studies on *TP53* mutations to the etiological factors for cancer of the oesophagus.]

(ii) Experimental systems

No data were available to the Working Group.

4.2.2 Oxidative stress

(a) Mate

(i) Humans

No data were available to the Working Group.

Table 4.3 Genetic and related effects of mate in non-human mammals in vivo

Species, strain, sex	Tissue	End-point	Test system	Result	Dose (LED or HID) (mg/kg bw)	Route, duration, dosing regiment	Comments	Reference
Male Wistar rats, *n* = 5/group	Blood leukocytes	DNA damage	Comet assay	–	4500–5400	Mate 2%, 8 weeks with drinking-water	Hot mate decreased DNA strand breaks induced by diethylnitrosamine by 50%	Silva et al. (2009)
Male Swiss mice free of specific pathogens, *n* = 10/group	Liver, kidney, and bladder cells	DNA damage	Comet assay	–	2000	Aqueous extract of roasted mate, 500, 1000 and 2000 mg/kg for 60 days	Decrease of H_2O_2-induced DNA strand breaks and improved DNA repair after H_2O_2 challenge in liver cells after ingestion of mate infusion	Miranda et al. (2008)
Male and female Wistar rats (*n* = 5 single treatment, *n* = 10 in multiple treatment group)	Bone marrow cells	Chromosomal damage	Chromosomal aberrations	–	2000	1000 and 2000 mg/kg bw per day (single dose) 1000 × 4 and 2000 × 4 mg/kg bw per day; 1000 or 2000 mg/kg fractionated in multiple doses		Fonseca et al. (2000)

–, negative; bw, body weight; HID, highest ineffective dose; LED, lowest effective dose

Table 4.4 Genetic and related effects of mate in non-mammalian cells in vitro

Test system	Strain	End-point	Results[a]		Dose	Comments	References
			Without metabolic activation	With metabolic activation			
Bacteria	*Salmonella typhimurium*, *TA97*, *TA98*, *TA100*, *TA102*	Reverse mutation	+ +	– TA100 + TA102	10 mg/plate	Negative result in TA97 and TA98 (not shown); no positive control and no SD	Fonseca et al. (2000)
Bacteria	*Escherichia coli* WP2sλ and RJF013	Prophage induction	+	–	50 mg/plate	No positive control and no SD	Fonseca et al. (2000)
Yeast	*Saccharomyces cerevisiae*	Lys induction	–	NT	Mate at room temperature	Concentration not given	Candreva et al. (1993)
			+	NT	Hot mate		

[a] +, positive; –, negative
HID, highest ineffective dose; LED, lowest effective dose; NT, not tested; SD, standard deviation

(ii) Experimental systems

Miranda et al. (2008) demonstrated a reduction of damage induced by ROS (H_2O_2) as a result of mate consumption. The mice were given an aqueous extract of roasted mate (0.5, 1.0, and 2.0 g/kg) for 60 days. In isolated liver cells subsequently exposed to H_2O_2, significantly reduced DNA damage was seen in cells from the mice that had received mate. Additionally, mate consumption enhanced DNA repair capacity of the cells, as assessed by use of a modified single-cell gel electrophoresis (SCGE) protocol.

Catalase and radical scavenging compound (dipyridyl), but not superoxide dismutase, reduced the genotoxic effects of mate in a bacterial test system (phage induction experiments with *E. coli*) (Fonseca et al., 2000).

(b) Hot beverages

No data were available to the Working Group.

4.2.3 Inflammation

(a) Mate

(i) Humans

Muñoz et al. (1987) conducted an endoscopic examination of the oesophagus in 30 regular hot mate drinkers and 30 controls matched according to age, cigarette smoking, and alcohol intake who drank mate no more than once per week. There was little difference in the prevalence of endoscopically diagnosed oesophagitis between the two groups. However, histological oesophagitis was found in 43% of mate drinkers versus 20% of controls ($P = 0.046$). There was also a higher prevalence of gastritis in the mate drinkers (in 20% of mate drinkers vs 13% of controls), but no P value was reported for this comparison.

(ii) Experimental systems

In a study of murine RAW 264.7 macrophages in vitro, mate extracts containing caffeoylquinic acid inhibited lipopolysaccharides-induced inflammation via suppression of nitric oxide and prostaglandin E2/cyclooxygenase-2 pathways (Puangpraphant et al., 2011).

(b) Hot beverages

In a study of tissue from 90 patients with cancer of the oesophagus, consumption of hot beverages was associated with increased levels of extracellular signal-regulated kinase 1 and 2 but not cyclooxygenase 2 (Yang et al., 2013).

4.2.4 Alterations of cell profileration or death

(a) Mate

(i) Humans

No data on exposed humans were available to the Working Group.

In an in vitro study, mate extracts containing caffeoylquinic acid inhibited proliferation of CRL-2577 (RKO) and HT-29 human colon cancer cells through induction of apoptosis. The Bax:Bcl-2 ratio was increased in HT-29 but not RKO cells. Caspase-8 activation leading to caspase-3 cleavage was seen in both cell types (Puangpraphant et al., 2011).

Gonzalez de Mejia et al. (2005) reported that a mate extract induced dose-dependent cytotoxicity in human squamous cancer cell lines (SCC-61 and OSCC-3).

(ii) Experimental systems

Cell proliferation decreased in liver and oesophageal tissue when room-temperature drinking-water containing mate (2%) was given to rats that had previously been given diethylnitrosamine and hot water (65 °C, 1 mL per rat) (Silva et al., 2009) for 8 weeks ad libitum.

In a clone-forming assay using yeast (*Saccharomyces cerevisiae*), a mate extract inhibited topoisomerase II but not topoisomerase I (Gonzalez de Mejia et al., 2005).

(b) Hot beverages

(i) Humans

No data were available to the Working Group.

(ii) Experimental systems

Rapozo et al. (2016) reported that water at 70 °C induced oesophageal necrosis in mice that healed and became resistant to necrosis from further exposures. However, water at 70 °C given together with NDEA interfered with epithelial regeneration, resulting in recurrent thermal injury and inflammation. Lower temperatures were without effect. Immunohistochemical analyses revealed that recurrent thermal injury induced basal cell proliferation (Ki67-positive cells), resulting in the expansion of epithelial basal cells (increased number of cytokeratin 14-positive cells and decreased number of cytokeratin 5-positive cells).

4.3 Other adverse effects

Several case reports documented thermal injury of the oesophagus upon ingestion of very hot beverages and food (Javors et al., 1996; Dutta et al., 1998; Eliakim, 1999; Choi et al., 2005; Go et al., 2007). Most of these studies reported various clinical signs of acute (single ingestion or short-term repeated exposure to very hot liquids or foods) injury to the epithelial lining of the oesophagus as the outcome of consuming very hot food, and stated that the prognosis was favourable with respect to the eventual healing of the injury. [The Working Group noted that these case reports indicate clinical symptoms upon acute injury by very hot foods or beverages, and no long-term follow-up was conducted.]

Roshandel et al. (2014) performed a cross-sectional study of 302 adults who were participants of the Golestan Cohort Study, a population-based cohort of 50 000 adults in the Islamic Republic of Iran, to examine potential risk factors of oesophageal conditions in asymptomatic subjects. Randomly selected participants underwent an endoscopic examination of the oesophagus. Lifestyle factor data, including drinking cold or hot tea, were obtained from

dietary questionnaires. [The Working Group noted that while the drinking temperature of tea was not specified, a publication by Islami et al. (2009b) from the same region indicated that drinkers of hot tea consume the beverages at temperatures above 60 °C.] The diagnosis of oesophageal squamous dysplasia in asymptomatic adults was not associated with drinking hot tea. A significant association was observed for the diagnosis of oesophagitis with drinking hot tea in comparison with drinking cold tea (30.9% incidence in cold tea drinkers and 39.1% in hot tea drinkers) only in multivariate analysis adjusted for other variables (OR, 2.27; 95% CI, 1.15–4.47). [The Working Group noted that the strengths of the study were the design and the use of endoscopy to establish the appropriate diagnosis; however, the major limitation was the small size of the study and difficulty with establishing what temperature of the beverage was considered "hot" by each subject.]

Sajja et al. (2016) conducted a study of lifestyle factors and risk of Barrett oesophagus in a cross-sectional study of 310 patients with histologically confirmed disease with 1728 individuals with no endoscopic or histopathological features of Barrett oesophagus. While risk of Barrett oesophagus was increased for subjects drinking hot or extremely hot coffee (OR, 1.47; 95% CI, 1.10–1.96) or cold tea (OR, 1.45; 95% CI, 1.12–1.86), no associations were found for drinking warm, hot, or extremely hot tea.

5. Summary of Data Reported

5.1 Exposure data

5.1.1 Very hot beverages

Beverages that are prepared at high temperatures most commonly include coffee, tea, mate, and other infusions. Such beverages are typically served at temperatures of 71–85 °C but are consumed at lower temperatures, typically 50–70 °C. Drinking temperature can be considered "hot" between 50 °C and 65 °C, and "very hot" at temperatures above 65 °C. However, there is considerable variation in drinking temperature depending on geographical region or culture, type of drink, and other factors such as the sex and age of the consumer. Average drinking temperatures also vary with the type of beverage: coffee is typically consumed "hot", while mate is often drunk "very hot". A wide range of drinking temperatures, varying from below 60 °C to over 70 °C depending on region and method of preparation, has been reported for tea.

Most epidemiological studies on the relationship between hot beverage consumption and cancer have relied on questionnaires to assess participants' preferences for drinking temperature, often by subjective categories such as "cold", "warm", "hot", or "very hot". Available data suggest good correlation between these subjective assessments and measured temperature. Data on other aspects, such as the average quantity and frequency of drinking per day and the total duration of drinking, are considered useful, but have not been reported in many studies.

5.1.2 Mate

Mate is an aqueous infusion prepared from dried leaves of *Ilex paraguariensis* (both the leaves and the infusion are known as mate). The major producers of mate leaves are Brazil, Argentina, and Paraguay. About 800 000 tonnes of leaves are produced annually worldwide. The consumption of mate has expanded to millions of consumers in South America, and also to some countries in North America, Europe, and the Middle East. The main importers are Uruguay, Syrian Arab Republic, Chile, and Brazil. Mate is usually drunk very hot (above 65 °C); in Paraguay and some regions of Brazil, however, it may be drunk cold. Mate preparations can use unroasted or roasted mate. Although mate leaves are used

primarily to prepare beverages, mate also has traditional medicinal uses; mate extracts can be found as ingredients of dietary supplements and energy drinks.

Among the numerous constituents, caffeine, and several chlorogenic acids have been identified in mate. Polycyclic aromatic hydrocarbons, including benzo[*a*]pyrene, may be formed during high-temperature processes such as drying or roasting/toasting, and have been reported at trace levels in the mate beverage.

5.2 Human carcinogenicity data

5.2.1 Drinking mate

(a) Cancer of the oesophagus

Data on the association of mate drinking with cancer of the oesophagus were available from nine case–control studies, most hospital-based, in South America. Some publications had overlapping data, so it is difficult to count the number of independent studies. A particularly informative pooled analysis of data from six South American case-control studies included 1400 cases of cancer of the oesophagus and 3229 controls. Careful adjustment was made for the potential confounders, including tobacco smoking and alcohol drinking, and a statistically significant trend of increasing risk of cancer of the oesophagus with increasing amount of mate consumed was observed. However, the exposure–response trend was found to vary by temperature, and it was only statistically significant for mate consumed hot or very hot, but not warm. Data on cold mate drinking were reported in one study in Paraguay, which found no evidence of increased risk of cancer of the oesophagus.

An evaluation of the amount of mate drinking independent of temperature was challenging, because mate is often drunk hot. However, the Working Group noted that a large pooled analysis did not show a statistically significant association between cancer of the oesophagus and drinking warm mate or the quantity of warm mate consumed. Furthermore, the pooled analysis of five case–control studies in South America found a similar magnitude of increased risk with hot mate and with other hot drinks. Another study found no increase in risk from drinking cold mate.

(b) Other cancers

Hospital-based case–control studies of the association of mate drinking with other cancers, including cancers of the upper aerodigestive tract, lung, urinary bladder, kidney, cervix, prostate, stomach, colon and rectum, and breast have been conducted in South America, most by a single research group in Uruguay. The majority of these studies considered cancers of the upper aerodigestive tract; very few studies were available for other cancer sites. In some studies drinking mate was associated with a higher risk of cancer of the larynx, other parts of the upper aerodigestive tract, bladder, kidney, cervix, lung, prostate, and stomach. For several cancer sites, drinking mate at a higher versus lower temperature was associated with an increased risk in a few studies. Because of the small number of studies for each type of cancer and the limitations of hospital-based case-control studies, the Working Group was unable to reach a conclusion as to the association of mate drinking with these diverse cancers.

5.2.2. Very hot beverages

(a) Cancer of the oesophagus

Data on associations of drinking hot beverages other mate were available from one cohort study, more than a dozen case–control studies, and a separate pooled analysis of five case–control studies in South America (all included in the pooled analysis of six studies above). The cohort study and most of the case-control studies showed increased risk of cancer of the oesophagus

with drinking hot or very hot tea compared with drinking tea at lower temperatures.

One case–control study observed an increased risk of cancer of the oesophagus for drinking very hot coffee compared with those drinking lower-temperature coffee, while the pooled analysis of five case–control studies in South America observed an increased risk from drinking very hot coffee with milk, but not for very hot coffee alone.

One cohort study, the pooled analysis of five case–control studies, and more than a dozen individual case–control studies investigated the association of cancer of the oesophagus and consumption of various combinations of very hot beverages, including tea and coffee, alcoholic drinks, and soup. The pooled analysis and about half of the case–control studies showed statistically significant positive associations between drinking hot beverages and risk of cancer of the oesophagus, whereas the cohort study and the remaining case–control studies did not show an association. The Working Group noted there was potential for information bias in the drinking temperature of tea as reported in the cohort study, however.

Three relatively recent systematic reviews have examined the association between drinking hot beverages and risk of cancer of the oesophagus. When summary statistics were calculated, the meta-odds ratio for the association of squamous-cell carcinoma of the oesophagus with consumption of drinks at higher versus lower temperatures was approximately 2.0 for drinking both mate and other hot drinks. There was no significant association with adenocarcinoma of the oesophagus.

The Working Group concluded that studies have shown a largely consistent association between drinking beverages at higher temperatures, versus lower temperatures, and risk of squamous cell carcinoma of the oesophagus. However, only one of the studies reporting a positive association was a prospective cohort study. Exposure assessment has mainly been based on the subjective description of temperature preference. Furthermore, the quality of adjustment for potential confounding was inconsistent across studies and possibility of information bias and publication bias cannot be ruled out.

(b) Other cancers

The few studies available on the associations between drinking beverages other than mate at higher versus lower temperatures and cancers of the upper aerodigestive tract, stomach, and skin gave mixed results. The available studies also have important limitations: all had case–control designs that varied by selection of controls, types of hot drinks assessed, temperature categories, and quality of adjustment for confounding factors. As a result of these limitations and the small number of studies for each cancer site, the Working Group was unable to draw conclusions about the association of cancers other than cancer of the oesophagus with drinking very hot beverages.

5.3 Animal carcinogenicity data

5.3.1 Mate

One co-carcinogenicity study in rats showed that cold mate given as drinking fluid significantly reduced the incidences of papillomas of the oesophagus and adenomas of the liver induced by hot water (65 °C) and *N*-nitrosodiethylamine.

5.3.2 Very hot water

One co-carcinogenicity study in mice and two co-carcinogenicity studies in rats (with one study in rats being considered inadequate for the evaluation) tested oesophageal tumour induction by local instillation of hot water only (50–70 °C for up to 37 weeks), with all studies giving negative results.

However, in the study in mice, hot water (at 70 °C, but not at 60 °C) increased the incidences of benign tumours and preneoplastic lesions of the oesophagus induced by *N*-nitrosodiethylamine. In the study in rats, hot water (at 65 °C, but not at 55 °C) enhanced *N*-nitrosomethylbenzylamine-induced squamous cell papilloma or carcinoma of the oesophagus (combined).

5.4 Mechanistic and other relevant data

5.4.1 Mate

Mate has many constituents; studies that used preparations or extracts from *Ilex paraguarensis*, rather than the individual components, were considered by the Working Group. Information on the pharmacokinetics and metabolism of individual components of mate is detailed in the monograph on Coffee Drinking in the present volume. No data from exposed humans on pharmacokinetics of these substances after oral ingestion of mate were available to the Working Group. In the only available study in rats of absorption and distribution, caffeine and caffeic acid, but not caffeoylquinic acid, were rapidly absorbed and distributed in systemic circulation after oral administration of an extract of mate constituents prepared differently from mate beverages. No information on the temperature of extract given or the concentration–time profiles was available. Only caffeic acid from hydrolysed mate extract was detected in liver, whereas no constituent was detected in brain or skin. In cell-free systems at 37 °C, mate preparations inhibited activity of human and porcine pancreatic lipase and human aromatase. No studies evaluated elimination kinetics of mate constituents.

The evidence is *weak* that mate is genotoxic. In two studies of mate drinkers that examined micronuclei induction in oesophagus and buccal swabs, no effect was reported. However, both studies had methodological limitations. Three studies in human cells in vitro did not provide consistent results for chromosomal alterations after direct exposure to mate. Three rodent in vivo studies of oral ingestion of mate solutions at room temperature for up to 60 days were negative for DNA strand breaks in lymphocytes, bone marrow, or other tissues. One study found a protective effect of mate on DNA strand breaks induced in the leukocytes in a study of diethylnitrosamine and hot water. One study in two bacterial test systems found a positive effect without, but not with, metabolic activation. In one study in yeast, no mutagenicity was detected with mate at room temperature, whereas hot mate was mutagenic.

Few data on other key characteristics of human carcinogens were available.

Few studies have reported other cancer-related adverse effects of drinking mate.

Overall, the mechanistic database on mate drinking is scant and only weak evidence for key characteristics of carcinogens or other effects is available.

5.4.2 Hot beverages

The evidence was *weak* that hot beverages are genotoxic. Hot beverage consumption (not otherwise specified) was associated with increased frequency of *TP53* mutation in primary oesophageal carcinomas in humans.

Few data on other key characteristics of human carcinogens were available for mate.

Several case reports have associated the consumption of hot beverages or foods with oesophageal injury. In addition, weak association has been found between consumption of very hot tea and oesophagitis in asymptomatic adults. One study of Barrett oesophagus found no association with drinking coffee or tea at any temperature, including hot or extremely hot.

Overall, the mechanistic data on hot beverages are scant.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of drinking very hot beverages. Positive associations have been observed between drinking very hot beverages and squamous cell carcinoma of the oesophagus.

There is *inadequate evidence* in humans for the carcinogenicity of drinking mate that is not very hot.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of very hot water at 65 °C or above.

There is *inadequate evidence* in experimental animals for the carcinogenicity of mate as a drinking fluid.

6.3 Overall evaluation

Drinking very hot beverages at temperatures above 65 °C is *probably carcinogenic to humans* (*Group 2A*).

Drinking mate that is not very hot is *not classifiable as to its carcinogenicity to humans* (*Group 3*).

6.4 Rationale

Rationale for the 2A evaluation of very hot beverages:

The epidemiological evidence for an association between drinking very hot beverages and human cancer has strengthened since Volume 51 with positive associations and trends in studies that considered various gradations of the temperature (e.g. cold, warm, hot, or very hot). Additionally, several experimental animal studies of initiation–promotion design conducted since 1991 demonstrate that hot water above 65 °C can act as a tumour promoter. While the mechanistic and other relevant evidence for very hot beverages is scant, there is biological plausibility of the association between drinking very hot beverages and cell injury, and the sequelae that may lead to cancer.

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