COFFEE[1]

1. Production and Use

1.1 Introduction

'Coffee has never been a mere beverage. Some three centuries have passed since it became the overnight rage among the fashionable and witty in cities throughout Europe. Even in the late twentieth century, however, it has yet to be relegated to the rank of the more pedestrian potions with which we quench our thirst or warm our insides. Little of coffee's original mystique has been worn off by centuries of familiarity.' (Hattox, 1988).

The year 575 is often cited as the date of the arrival of coffee on the Arabian peninsula from Ethiopia. Commercial and political links were at that time becoming quite strong across the Red Sea. Coffee cherries (*bun* or *bon*) were then probably only dried and chewed as a stimulant against fatigue. It is only by the middle of the fifteenth century that coffee as a beverage (*kahwah* in Arabic), an infusion of roasted and ground coffee beans that had been cultivated in the Yemen, near the harbour of Mocha, came into general use throughout the Ottoman empire. By the end of the sixteenth century, it had crossed the Mediterranean Sea, and in less than a century it had spread throughout Europe and to the British settlements in North America (Wellman, 1961).

During the seventeenth century, the cultivation of coffee spread to the Malabar coast of India and to Ceylon; and, from the beginning of the eighteenth century, seedlings of *Coffea arabica* L. cultivated in European glasshouses, as first described by Linnaeus in 1737 (Debry, 1989), were introduced into the Dutch West Indies and to the Portuguese, French and Spanish colonies of Asia and America (Wellman, 1961).

Low-altitude coffee cultures in Asia were destroyed during the last part of the nineteenth century by the coffee rust, *Hemileia vastatrix*. A rust-resistant species,

[1]Unless otherwise specified, the term 'coffee' is used to mean brewed, caffeinated coffee.

Coffea canephora, var. *robusta*, was introduced during the twentieth century in Asia, Africa and, more recently, Brazil (Viani, 1986).

1.2 Production processes

(*a*) *Green coffee*

(i) *Botany and culture* (Wrigley, 1988; Viani, 1989)

Approximately 60 species of the genus *Coffea* L. (Rubiaceae family) have been described. The commercially important varieties are *C. arabica* L., arabica coffee, which accounts for 85-90% of world production, and *C. canephora* (Pierre ex Froehner), robusta coffee, which contributes 10-15% of world production. Two other species, which contribute less than 1% of world production, are also grown: *C. liberica* (Bull ex Hiern), liberica coffee, and *C. dewevrei* (de Wild.), excelsa coffee.

The main characteristics of arabica and robusta coffees are given in Table 1.

Table 1. Main botanical and physical characteristics of arabica and robusta coffee plants[a]

Parameter	Arabica species	Robusta species
Botanical varieties, mutants and cultivars	Arabica or typica bourbon, Caturra, Maragogipe, etc.	Robusta (upright), nganda (spreading), Kouilouensis (various spellings: kouilou, quillou, conilon), etc.
Optimal growth		
Climate	Temperate, equable	Warm, humid
Altitude (m)	700–1700	0–800
Average temperature (°C)	15–23	18–27
Maximal temperature (°C)	25	30
Rain/year (mm)	1500–2200	2200–3000
Plant	Self-fertilizing	Sterile
Chromosomes (2n)	44	22
Root system	Deep	Shallow
Leaf	Small, glossy, oval	Large, broad, corrugated
Flower (white to pink)	After rain, small	Irregular, large
Fruit, cherry or berry (crimson), 60–65% water	Oblong ellipsoid, 15 mm long, 8–9 months to ripen	Ellipsoid, 12–mm long, 10–11 months to ripen
Seed, bean (blue-green to yellow-green), 10–12% water	Round to oval, flat, deeply grooved, 5–13-mm long	Oval to round, grooved, 4–8-mm long
Caffeine content of seed (% dry basis)	0.8–1.4, average 1.2	1.7–4.0, average 2.0
Weight of clean beans from fully ripened cherries (%)	12–20 (usually 16–18)	17–22 (usually >20)

Table 1 (contd)

Parameter	Arabica species	Robusta species
Density of beans (g/l)	550–700	550–700
Pests (diseases)[b]		
Hemileia vastatrix (rust)	Susceptible	Resistant
Colletotrichum coffeanum (coffee berry disease)	Susceptible	Resistant
Stephanodores coffeae (*Hypothenemus hampei*) (coffee berry borer)	Susceptible	Susceptible

[a]From Viani (1986, 1989)

[b]From Clarke & Macrae (1988a)

The seeds of arabica and cuttings of robusta coffee plants are propagated in nurseries and are cultivated on sheltered slopes, protected from wind and frost on porous, well-drained soil rich in organic matter and slightly acidic.

Natural and botanical interspecific hybrids have been described: 'Hibrido de Timor' is a natural cross between arabica and robusta, while arabusta and *Icatu* were created artificially (Wrigley, 1988).

(ii) *Harvesting and processing of coffee cherries* (Viani, 1986, 1989)

The operations necessary to transform harvested cherries into green beans vary depending upon ecological conditions. Where water is scarce or labour unskilled, the 'dry' process is applied; such is the case in Brazil and Ethiopia, the main producers of 'natural' unwashed arabicas and most robustas. Where all cherries can be picked at the optimal degree of ripeness, where water is abundant and equipment is available, coffee is treated by the 'wet' process, resulting in 'washed' arabicas. The two processes are shown schematically in Table 2.

In the 'dry' or 'natural' process, cherries of different degrees of ripeness are strip-picked and handled simultaneously. They are spread in a thin layer on the ground, where they are sun-dried for up to three weeks. Husks (skin and pulp) are removed in centrifugal hulling machines.

In the 'wet' or 'washed' process, freshly picked berries are separated in water channels into 'floaters' (overripe and one-bean cherries) and 'sinkers' (ripe cherries), which are pulped mechanically; floaters are usually dry-processed and consumed locally. Enzymatic fermentation of the mucilage which still adheres to the bean solubilizes the mass so that it can be removed by stirring with water. Some pulpers remove skin, pulp and mucilage mechanically in a single operation. The beans, which are still surrounded by parchment, are then washed and either

sun-dried for four to eight days or dried in a hot-air dryer for 24-30 h. The parchment is removed in centrifugal hulling machines, and the beans are cleaned by density, sorted electronically by colour, graded by size through screens and bagged in 60- or 70-kg jute bags.

Table 2. Dry and wet processes for processing coffee cherries[a]

Operation	Dry	Wet
Harvesting of cherries	strip	selective
Floating in water	no	yes
Pulping of 'sinkers'	no	yes
Fermenting	no	yes
Washing	no	yes
Drying	yes	yes
Hulling	yes	yes
Polishing	no	usually
Cleaning	yes	yes
Sorting/grading	usually	yes
Bagging	yes	yes

[a]From Viani (1989)

(*b*) *Decaffeination* (Viani, 1986, 1989)

The presence of water is essential in decaffeination in order to open the cellular structure of the bean and to ensure diffusion of caffeine out of the bean by solubilizing the caffeine-potassium chlorogenate complex. Decaffeination is usually performed on green beans before aromatic substances are formed by roasting; however, a process for decaffeinating roasted coffee extract is also used. The techniques applied can be divided approximately into two types: 'bean decaffeination' at moisture levels below 40% and 'extract decaffeination' at moisture levels above 60%.

(i) *Solvents/adsorbents*

The solvents and adsorbents currently employed during decaffeination are: dichloromethane (see IARC, 1986a, 1987), ethyl acetate, edible fats and oils, supercritical carbon dioxide and acid-activated carbon. Formerly trichloroethylene (see IARC, 1979, 1987) was used.

(ii) *Bean decaffeination*

This technique was patented in 1905 by Roselius (Meyer, 1906; Meyer *et al.*, 1908; Katz, 1987) and is still the most commonly used. Green coffee beans are

swollen to contain 30-40% moisture with water and steam at temperatures of 20-100°C for up to 5 h and decaffeinated in static or rotating drums with a water-saturated solvent, such as dichloromethane (Patel & Wolfson, 1972), ethyl acetate (Morrison & Phillips, 1983) or edible fats and oils (Malizia & Trumbetas, 1984; Pagliaro *et al.*, 1984), at temperatures ranging from 60 to 105°C for 2-12 h, depending upon the level of residual caffeine permitted. Most countries require that the content be reduced to less than 0.1% on a dry weight basis. The beans are then freed from residual volatile solvent (deodorized) by steam stripping at 100-110°C for 1-4 h to levels usually well below those required by local regulations (< 5-15 ppm according to country and solvent), and dried to their initial moisture content (approximately 10%) at 40-48°C for 0.5-10 h with hot air or under vacuum.

The solvent is recovered by batch or continuous evaporation or by steam stripping of the caffeine under vacuum, and the caffeine is purified by repeated crystallization for further use in, e.g., cola-type drinks.

Green coffee beans can also be decaffeinated using supercritical carbon dioxide at temperatures and pressures above its critical point (31.06°C, 73.8 bar), usually at 40-80°C and 200-300 bar for 5-30 h (Zosel, 1981; Martin, 1982). Supercritical carbon dioxide is circulated in a pressurized vessel through moist coffee, where it dissolves the caffeine selectively; the caffeine solution is then passed through a second pressurized vessel containing activated carbon or water which retains the caffeine.

(iii) *Extract decaffeination*

Green (or roasted) coffee beans are extracted with water (Berry & Walters, 1943), and the extract is decaffeinated either by liquid-liquid extraction with dichloromethane (Katz, 1980) followed by steam deodorization or by selective adsorption of caffeine on acid-activated carbon. Processes that do not employ an organic solvent are known as 'water decaffeination'.

The decaffeinated extract is concentrated and reincorporated on the predried decaffeinated beans (Fischer & Kummer, 1979; Green & Blanc, 1981). Alternatively, the decaffeinated extract can be used to decaffeinate new beans (Katz & Proscia, 1981). The beans are then dried to their initial moisture level.

(*c*) *Roasted coffee* (Rothfos, 1986)

(i) *Process*

During the roasting process, hard green coffee beans which are stone-hard increase in volume and develop a brittle structure, a dark-brown colour and a characteristic flavour rich in volatile constituents. During the first phase of roasting, the beans are dried at temperatures of up to 120-150°C, after which

pyrolysis starts. The release of carbon dioxide and volatile aroma increases at temperatures above 150°C. In the last phase of roasting, when the temperature reaches approximately 190°C, the reaction becomes exothermic and the beans puff, doubling in size.

The chemical constituents of green beans can change dramatically with roasting. For example, the total chlorogenic acid content of green arabica coffee beans is typically 6.9%; following light roasting, the concentration decreases to about 2.7%, and after dark roasting is only about 0.2% (Trugo & Macrae, 1984a).

After cooling, which can be accelerated by quenching with water, residual carbon dioxide trapped in the bean is released slowly over a period of days.

The main operations used in the manufacture of roasted coffee are shown in Table 3.

Table 3. Main operations in the manufacture of roasted coffee

Operation	Means
Reception	Green coffee arrives at the plant either loose in containers or in bags.
Emptying	Manually or mechanically
Weighing	In hoppers of 250- or 500-kg capacity
Cleaning	Through vibrating screens (removal of small stones and large, heavy bodies); by air levitation (removal of dust); with magnets (removal of iron scrap)
Conveying	Pneumatically, to storage silos
Storage	In bins of 1- to 100-tonnes capacity
Weighing	Manually or automatically for blending
Blending	Manually (1-2 bags max.) or mechanically (up to 10 different coffee types)
Roasting	In batch or continuous roasters (a few to 5000 kg/h)
Weighing	To determine the roast weight loss
Conveying	With bucket (vertically) or belt conveyors (horizontally) or with dense-phase air conveyors to avoid breakage
Sorting	Electronically by colour
Degassing	Freshly roasted coffee releases carbon dioxide: the gas must be allowed to escape before whole coffee beans are packaged in gas-tight wrappings
Grinding	In stainless-steel mills
Packaging or Processing	Under vacuum or inert gas to maintain freshness In instant coffee plants

(ii) *Roasters*

Many models of roasters exist, which operate both by batch and continuously, with capacities ranging from a few kilograms to over 5000 kg/h, and range from

manually operated to fully automated. They can be divided into conduction roasters with direct-flame heating and convection roasters employing preheated gas. Modern gas-heated roasters are equipped with gas recirculation units and catalysts to reduce emissions. Some models are also equipped with automatic cleaning cycles to avoid a build-up of tars (Viani, 1986).

In some of the more recent models, so-called 'high yield' or 'fast roasted' coffee can be prepared by heating green coffee beans by convection to temperatures of up to 300°C for 2-3 min and by increasing the ratio of hot air to beans. This type of roasted coffee can yield up to 20% more extractable matter with a sharper taste when brewed.

(iii) *Grinders*

Roasted beans are ground in mills that vary in capacity from a few grams to 4 tonnes/h. The average particle size of the ground coffee depends on the extraction equipment to be used; indicative sizes are given in Table 4.

Table 4. Particle sizes of roasted coffees[a]

Use	Particle size (mm)
Instant coffee manufacture	1.5 to whole beans
US drip, percolator	0.7–1.0
Filter	0.4–0.6
Espresso	0.3–0.4
Middle East	<0.1

[a] From Viani (1986)

(iv) *Packaging*

Unlike green beans, roasted coffee spoils relatively quickly if unprotected from oxygen and moisture; at ambient temperature, whole beans become stale after four to six weeks and ground coffee after two weeks.

Since coffee beans release carbon dioxide for up to 48 h after roasting, they cannot be packed in airtight containers immediately. Whole beans are therefore either placed in non-airtight packs or allowed to degas and then packed under vacuum or in an inert atmosphere in metal cans or impermeable plastic containers. Coffee is now sold pre-ground and packed in brick packs or cans after short degassing (2-4 h) or under an initial slight vacuum in flexible bags with a one-way degassing valve (Viani, 1986).

(*d*) *Instant coffee* (Viani, 1986)

The first commercially acceptable instant (or soluble) coffee was produced in Switzerland in 1938 as 50% coffee solids and 50% corn syrup solids; 100% pure instant coffee became available from the 1950s.

Instant coffee is the dried water extract of roast and ground coffee, which readily dissolves in both cold and hot water and eliminates the need for brewing equipment. The unit operations performed during the manufacture of instant coffee are: storing, blending, decaffeination and roasting of green beans; grinding, recovery of volatile aroma and extraction of roasted beans; stripping of aroma; concentrating and drying of the extract; and agglomeration, aromatization and packaging of the powder. The operations performed on the beans up to and including roasting have already been described. The steps described below are specific to instant coffee technology.

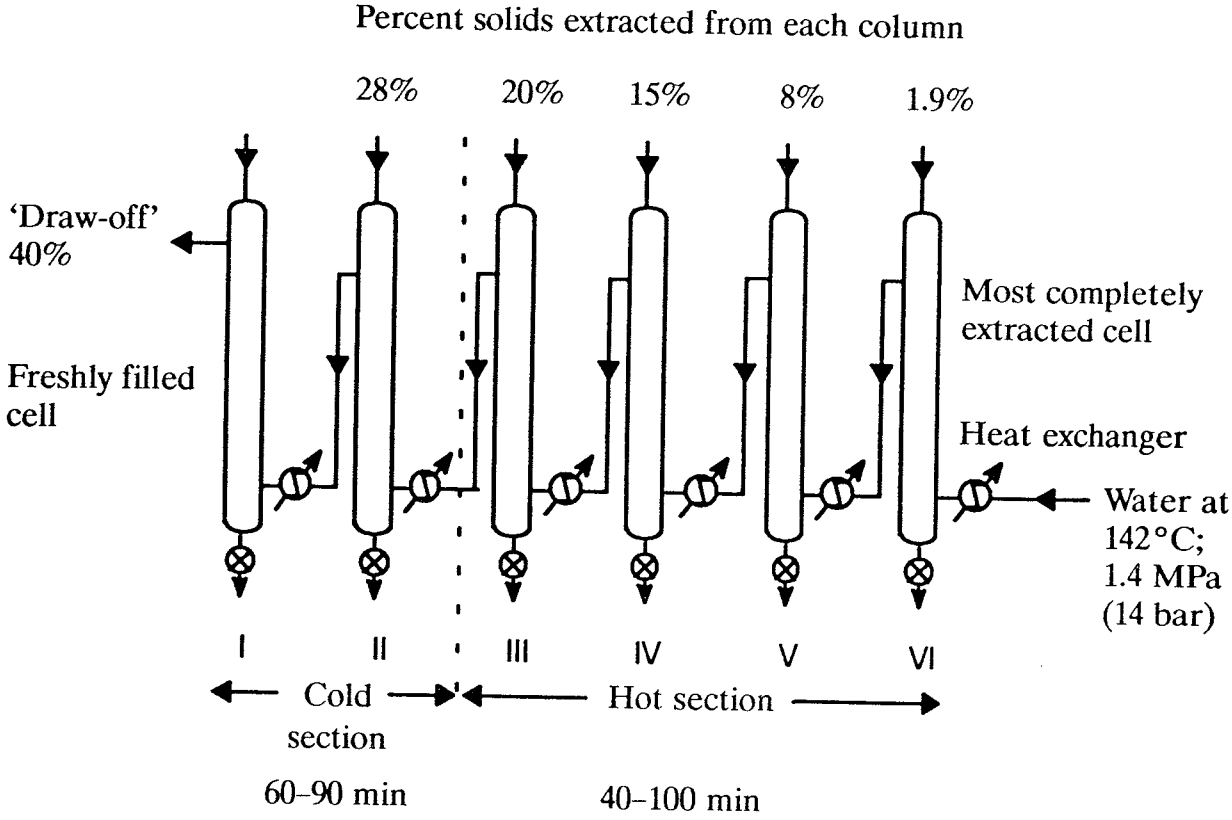
(i) *Extraction*

Whole roasted coffee beans or coffee ground to a particle size of 1.5 mm are extracted with softened water in a battery of five to eight percolation columns called 'cells', with a capacity of a few kilograms to one tonne. The process is semi-continuous; water at 160-180°C enters the most completely extracted cell and circulates through to the most recently filled cell (see Figure 1). The cells are divided into 'hot' cells at a temperature of 140-180°C under a pressure of 14-16 bar and 'cold' cells at a temperature of approximately 100°C. In the hot cells, high-molecular-weight material (in particular carbohydrates) is extracted. In the cold cells, the material with the most flavour is extracted. The extract is withdrawn from the fresh cell, cooled to 4-5°C and sent into a scale in amounts that depend on the desired yield (33-55% based on roasted coffee) and on the concentration of the extract (10-30%). At the end of the 'draw-off' period, a new cell enters the circuit, which may have been steam-stripped to recover volatile aroma, and the spent grounds are evacuated from the most completely extracted cell.

(ii) *Concentration*

Extracts with a concentration of 25-30% (w/w) soluble solids can be dried directly but with loss of volatile components. The volatile constituents present in extracts coming from the hot section are, however, unimportant from the point of view of aroma or flavour. The hot extract can then be evaporated to a concentration of 50-60% (w/w) and mixed with cold extract; if both hot and cold extracts are collected together, the dilute extract is stripped prior to concentration and the volatile components added back ('standardization') before drying. A technique that preserves most of the volatile aroma is freeze concentration, in which pure ice is

Figure 1. Battery for instant coffee extraction[a]



[a]From Viani (1986)

separated from the frozen extract in gradient columns at a concentration of up to 35-40%. The extract is then cooled to 4-5°C and clarified.

(iii) *Spray-drying*

The extract is sprayed through a pressure nozzle into the top of a tower and dried by a concurrent flow of hot air at approximately 250°C; the dry powder is collected at the bottom of the tower. Powder with a bulk density of 230-300 g/l can thus be obtained. For the convenience of consumers, the powder can be agglomerated to a coarse structure by rewetting and redrying.

(iv) *Freeze-drying*

The extract is gradually frozen to –40 to –50°C; ice crystals are separated and sublimed under vacuum.

(v) *Aromatization*

The volatile aroma fractions collected during stripping of the fresh cell can be emulsified with oil from pressed roasted coffee or spent grounds and sprayed or injected onto the powder at levels of 0.3-1.0% (w/v) during packaging.

(vi) *Packaging*

The powder, which should contain less than 5% moisture (Commission of the European Communities, 1985), is packed under vacuum or in an inert atmosphere in jars or flexible bags and is stable for more than two years if unopened.

1.3 Worldwide production, trade and consumption

(*a*) *Production and export*

Coffee is one of the major commodities of world trade; it is often the main source of foreign exchange for the producing countries in the belt between the tropics. World coffee supply and distribution in 1984-88 are given in Table 5.

Table 5. World production and distribution of coffee in 1984-88 (millions of 60-kg bags [millions of tonnes])[a]

Year	Total production	Domestic consumption	Total exports
1984	83.8 (5.03)	19.4 (1.16)	64.4 (3.86)
1985	90.0 (5.40)	19.2 (1.15)	70.8 (4.25)
1986	81.1 (4.87)	19.8 (1.19)	61.3 (3.68)
1987	107.7 (6.46)	18.6 (1.12)	89.1 (5.35)
1988	87.1 (5.23)	19.7 (1.18)	67.5 (4.05)
Average	89.9 (5.39)	19.3 (1.16)	70.6 (4.24)

[a]From International Coffee Organization (1989a)

International coffee trade is regulated by the International Coffee Organization, which administers the International Coffee Agreement. The current 1983 (International Coffee Organization, 1982) agreement expired in September 1989 but was extended for a further two years as of October 1989. It has been signed by 74 members — 50 exporting and 24 importing countries comprising 99% of world production and 85% of world consumption (International Coffee Organization, 1989b,c). The producing countries are divided into three main categories, according to botanical origin (arabica or robusta) and method of preparation (dry or wet processing). The majority of the coffee produced is traded as milds (wet-processed arabica), Brazilian and other arabicas (dry-processed arabicas) and robustas (dry-processed) (Viani, 1989).

The production, exports and consumption of green coffee by the main producing countries are given in Table 6. The consumption figures are only indicative, as they were calculated by dividing the amount of coffee that

disappeared (produced but not exported, 1984-87 average) by the 1987 population of the country concerned (Anon., 1989).

Table 6. Production, exports (millions of 60–kg bags) and consumption of green coffee (kg *per caput* per year) of the main producing countries[a]

Country	Production[a] (1984–88 average)	Exports[b] (1983–88 average)	Consumption[c]
Wet–processed arabicas	42.16	29.93	
Colombia	14.25	10.49	3.64
Mexico	4.93	3.25	1.36
Guatemala	2.85	2.46	1.29
India	2.78	1.41	0.07
Costa Rica	2.24	1.94	5.06
El Salvador	2.19	2.61	1.66
Kenya	1.88	1.65	0.08[d]
Ecuador	1.82	1.59	2.13
Honduras	1.41	1.31	2.37
Peru	1.20	1.03	0.60
Venezuela	1.06	0.18	2.60
Dominican Republic	0.85	0.52	2.88
Tanzania, United Republic of	0.78	0.79	0.01[d]
Nicaragua	0.72	0.70	1.88
Others	3.20	–	
Dry–processed arabicas	28.93	18.46	
Brazil	26.13	17.14	3.10
Ethiopia	2.80	1.32	2.09
Robustas	16.23	16.27	
Indonesia	6.01	4.76	0.41
Ivory Coast	4.35	3.84	1.24
Zaire	1.86	1.52	0.38
Madagascar	1.11	0.81	1.31
Philippines	1.02	0.49	0.51
Others	1.88	4.85	
Total	87.32	64.66	

[a] From International Coffee Organization (1989b,d)
[b] From International Coffee Organization (1989e)
[c] Calculated by the Working Group
[d] From Viani (1989)
–, not available

(*b*) *Imports and consumption*

The disappearance (industry term: net imports adjusted for changes in visible inventories; in millions of 60-kg bags) and consumption (disappearance divided by the population of the country in 1987; in kg *per caput* per year) of green coffee in the main importing members of the International Coffee Organization are given in Table 7.

Per-caput disappearance of coffee in importing member countries of the International Coffee Organization in 1981-86 is given in Table 8. Annual per-caput consumption of coffee in major consuming countries in 1970-81 is given in Table 9.

Imports (in millions of 60-kg bags) and estimated consumption (in kg *per caput* per year) of green coffee by non-International Coffee Organization member consuming countries importing more than 100 000 bags per year are given in Table 10.

(*c*) *Brewing techniques* (Pictet, 1987)

The most common brewing techniques are indicated below. Extraction yields of 16-30% (w/w) for the so-called 'super-high-yield' coffees are usual, depending on the type of roasting, contact time and pressure and fineness of grind. Brewing techniques encompass a wide range of procedures used in different parts of the world, which are based on the types of coffee and roasting procedures traditionally used. Local cultural practices associated with the preparation and use of coffee result in a wide range of individual consumption patterns.

(i) *Decoction/boiling*

To prepare northern Scandinavian 'boiled' coffee, roasted ground arabica coffee is brewed in continuously boiling water. The brew is made by boiling about 70 g coffee grounds in 1 l boiling water for 10-30 min (1 cup ~ 150 ml). The decoction usually lasts upwards of 10 min. Sometimes, fresh coffee and water are added to a boiling kettle during the day.

Very finely ground Turkish coffee (less than 0.1 mm particle size) is brewed by gentle boiling of proportions of 5 g coffee grounds, 10 g sugar, 60 ml water until a foam is formed (1 cup ~ 60 ml).

(ii) *Infusion*

Light-to-medium roasted, coarsely ground coffee (particle size, 0.7-1.0 mm) is infused with boiling water in a pot for a few minutes, stirred and separated from the grounds by pouring through a metal strainer. In the 'plunger' system, the metal strainer is pushed down the coffee pot to separate the grounds from the coffee. This system is used in northern Europe and Australia with a concentration of grounds to

Table 7. Disappearance (millions of 60–kg bags) and consumption [calculated by the Working Group] of green coffee in main importing countries by order of consumption (average, 1984–1988)

Country	Disappearance[a]		Consumption (kg *per caput* per year)	Coffee used in 1988 (%)[b]		
	1984–88 average	1989		Arabica	Robusta	Other
Finland	1.00	1.01	12.24 stable (10–11 in 1988)[b]	99	1	
Sweden	1.60	1.47	11.57 down	99	1	
Denmark	0.92	0.89	10.83 down (10–11 in 1988)[b]	80	17	3
Norway	0.71	0.69	10.12 stable (10 in the 1980s)[b]	97	2	1
Netherlands	2.38	2.34	9.65 stable (8.13 in 1988)[b]	68	27	5
Austria	0.98	1.31	7.88 up (8.7 in 1988)[b]	87	12	1
Germany, Federal Republic of	7.68	9.02	7.60 up (7.92 in 1988)[b]	89	10	1
Belgium/Luxembourg	1.23	1.11	7.52 stable	NA		
Switzerland	0.73	0.87	6.46 down	81	17	2
France	5.16	5.18	5.63 up	45	54	1
USA	18.09	18.69	4.48 down	81	15	4
Italy	4.22	4.30	4.41 up	52	48	
Canada	1.82	1.83	3.33 down	NA		
Spain	2.06	2.50	3.17 stable (2.7)[b]	58	41	1
Cyprus	0.03	0.04	2.77 NA	NA		
Greece	0.45	0.56	2.77 stable (2.75 in 1987)[b]	94	5	1
UK	2.33	2.24	2.49 up	57	42	1
Australia	0.64	0.65	2.39 up	NA		
Japan	4.57	4.80	2.25 up	NA		
Portugal	0.40	0.45	2.04 up (2.2)[b]	30	62	8
Yugoslavia	0.65	0.74	1.67 NA	NA		
Ireland	0.10	0.10	1.46 stable	NA		
Total	57.75	60.79				

[a] From International Coffee Organization (1989f, 1990)
[b] According to Müller-Henniges & Rothfos (1989)
NA, not available

water of up to 65 g/l. In North America, this method is used with high-yield, lightly roasted coffee with grounds concentrations of 28-40 g/l. One cup equals 150-190 ml.

Table 8. Derived per-caput disappearance of coffee in importing member countries of the International Coffee Organization, 1981–86[a]

Importing member	Kilograms green coffee equivalent for total population					
	1981	1982	1983	1984	1985	1986
USA[b]	4.80	4.77	4.63	4.71	4.65	4.41
EEC						
Denmark	11.79	11.46	11.15	11.05	11.04	11.00
Netherlands	9.09	8.97	9.58	9.46	9.41	9.65
Germany, Federal Republic of	7.06	7.34	7.29	7.03	6.84	7.38
Belgium/Luxembourg	8.58	7.15	8.84	7.25	7.60	7.14
France	6.05	5.91	5.94	5.39	5.47	5.49
Italy	3.98	4.33	4.34	3.89	4.93	4.37
Spain	2.75	2.76	3.19	2.92	2.74	3.44
UK	2.55	2.43	2.41	2.51	2.44	2.42
Greece	2.63	2.65	2.81	3.00	2.96	2.18
Ireland	1.10	1.00	1.16	1.47	1.59	1.81
Portugal	1.48	1.42	1.90	1.96	2.19	1.64
Other importing members						
Finland	13.52	12.78	12.93	14.59	10.09	12.09
Sweden	12.91	11.73	12.14	11.29	11.55	11.64
Norway	10.26	10.51	11.36	10.39	10.47	10.09
Austria	6.55	7.92	8.53	7.73	7.34	7.75
Switzerland	6.57	5.58	6.00	6.04	6.17	6.59
Canada	4.79	4.33	4.25	4.27	4.41	4.15
Singapore	[c]	[c]	[c]	2.36	[c]	[c]
Yugoslavia	2.01	1.05	1.51	0.89	0.58	2.31
Australia	2.51	2.62	2.31	2.44	2.11	2.24
Japan	1.68	1.85	1.94	2.01	2.14	2.23
New Zealand	2.09	1.96	2.25	2.01	1.94	1.88
Cyprus	2.95	2.63	6.55	[c]	2.87	1.34
Fiji	0.37	0.18	0.18	0.17	0.09	0.09

[a] From Clarke & Macrae (1988b)

[b] Based on estimates of civilian population by the US Department of Commerce

[c] Re-exports exceeded imports in these years.

Table 9. Per-caput coffee consumption per year in major consuming countries[a]

Country	Per-caput consumption in green bean equivalents (kg)								Ratios to 1970	
	1970	1975	1976	1977	1978	1978–79	1979–80	1980–81	1977	1980–81
Finland	14.13	13.72	15.18	10.54	11.72	13.22	12.46	12.41	0.75	0.88
Sweden	13.15	14.10	14.03	8.59	12.13	11.92	12.10	11.92	0.65	0.91
Denmark	12.88	13.02	12.14	10.75	11.00	10.50	11.03	11.59	0.83	0.90
Norway	10.10	9.74	10.33	7.20	11.14	10.02	9.80	10.11	0.71	1.00
Belgium	6.61	6.96	8.74	5.67	7.12	8.33	7.17	8.91	0.86	1.35
Netherlands	6.97	9.41	9.63	5.53	7.38	8.51	7.84	8.36	0.79	1.20
Germany, Federal Republic of	4.86	5.65	5.87	5.73	5.94	6.47	6.45	7.04	1.18	1.45
Austria	3.73	4.88	4.99	4.15	4.82	5.66	6.54	6.54	1.11	1.75
Switzerland	5.58	6.93	6.47	5.25	5.28	5.30	5.91	6.50	0.94	1.17
France	4.71	5.65	5.47	5.01	5.58	5.75	5.67	6.24	1.06	1.32
Canada	4.27	4.33	4.38	3.52	4.23	4.54	4.28	4.86	0.82	1.14
USA	6.23	5.62	5.82	4.34	4.94	5.13	4.59	4.68	0.70	0.75

[a] From Gilbert (1984)

Table 10. Imports and consumption of green coffee in main non-International Coffee Organization member consuming countries, by order of consumption (average, 1982–86)[a]

Country	Imports (millions of 60-kg bags)	Consumption[b] (kg *per caput* per year)
German Democratic Republic	1.08	3.94
Hungary	0.65	3.83
Lebanon	0.18	3.38
Algeria	1.10	2.31
Czechoslovakia	0.44	2.09
Saudi Arabia	0.39	1.93
New Zealand	0.11	1.91
Argentina	0.60	1.08
Poland	0.52	0.99
Bulgaria	0.13	0.83
Syria	0.12	0.61
Korea, Republic of	0.28	0.55
South Africa	0.27	0.49
Chile	0.10	0.43
Morocco	0.22	0.40
Hong Kong	0.06	0.33
Korea, Democratic People's Republic of	0.13	0.32
USSR	0.84	0.23
China	0.03	–
Others	0.67	–
Total	7.92	

[a] From International Coffee Organization (1989g)

[b] Estimated by the Working Group by dividing the quantity of green coffee imported by the country during the 'coffee year' 1987–88, less the average re-exports of 1985–87, by the population of the country in 1984

–, not available

(iii) *Filtration*

Filtered coffee, generally known as 'drip coffee' in North America, is made by pouring boiling water over finely ground, light-to-dark roasted coffee (average particle size, 0.5-0.7 mm) in a filter paper set in a funnel. The brew drips into a warmed pot within about 2-5 min. Automatic coffee makers are now used in most central and northern European, North American and Japanese households; the system is also widely adopted for food-service coffee-making equipment. Brew strengths vary according to the degree of roasting, the process and local habits;

concentrations as high as 75-80 g/l (dark roast; 1 cup ~ 60-150 ml) are common in France and Brazil. For automatic coffee makers, concentrations of 28-65 g/l are used.

(iv) *Percolation*

Coarsely ground coffee (average particle size, 0.7-1.0 mm) is extracted by recirculating boiling water until the desired brew strength is reached. In more modern equipment, continuous recirculation and filtration by gravity (under pressure) improve extraction and shorten brewing time to under 2 min. The use of percolators has declined significantly in favour of automatic drip coffee makers. Ground coffee concentrations normally used range from 40 g/l (light roast) in North America to 60 g/l (medium roast) in the UK.

(v) *Vaporization under pressure* (espresso)

Water heated to just above boiling-point is forced by slight excess pressure through a bed of medium-to-dark roasted coffee ground to an average particle size of 0.3-0.4 mm ('mocca' or 'Neapolitan' coffee machines). This method is used in most Italian and Spanish households. In Italian 'espresso' machines, the addition of a high-pressure pump working at 8-12 bar allows rapid extraction of grounds during 15-35 sec at a water temperature of 92-95 °C. For 5-8 g of roasted coffee, one 25-60 ml cup is obtained with an extraction yield of coffee soluble solids from the roasted coffee of 18-26% and a soluble solids concentration in the cup of 20-60 g/l brew; 70-85% caffeine is recovered (Petracco, 1990).

(vi) *Instant coffee*

Average concentrations used in most countries are 1.5-2.5 g/150 ml cup, although in Latin countries, 2 g/60 ml cup are common. Consumption in the ten countries where the most instant coffee was drunk in 1987 is given in Table 11.

(d) Consumption in selected countries

Worldwide consumption of green coffee (1983-87 average) can be estimated at 1 million tonnes of arabica and 200 000 tonnes of robusta in producer countries and 2.9 million tonnes of arabica and 1 million tonnes of robusta in consumer countries, giving a total of 5.1 million tonnes per year. Using a conversion factor of 1.19 kg green coffee for each kilogram of roasted coffee (International Coffee Organization, 1982), the total quantity of roasted coffee consumed per year is thus 4.29 million tonnes.

Table 11. Consumption of instant coffee in the ten countries where the most was drunk in 1987[a]

Country	Retail sales (tonnes)	Share of total coffee market (%)
USA	55 090	33
UK	37 500	94
Japan	34 200	86
France	19 850	32
Mexico	19 380	71
South Africa	16 970	91
Australia	9 820	96
Canada	8 540	52
Germany, Federal Republic of	8 400	10
Spain	7 600	37

[a] From Viani (1989)

On the basis of a caffeine content of 1.1% for green arabica and 2.2% for green robusta, with no loss due to either decaffeination or processing, worldwide consumption of caffeine from coffee can be estimated to be 65 500 tonnes per year (1983-87 average), which is equivalent to 40 mg per day *per caput*. This figure corresponds to just over half of the caffeine consumed from all sources (Roberts & Barone, 1983; Gilbert, 1984; Simpson, 1988).

Data on actual coffee or caffeine consumption are often based on the reported number of cups per day; but the wide variability in volume and strength of a 'cup' of brewed coffee renders such data difficult to interpret. The actual variation of 'cups' has been reported in several studies in North America. According to a study in Canada (Stavric *et al.*, 1988), one household cup equals approximately 225 ml but can vary between 25 and 330 ml, with mean caffeine contents of 84, 71 and 82 mg/cup for drip, instant and percolated coffee, respectively. In another study in Canada (Gilbert *et al.*, 1976), cup size varied between 140 and 285 ml, with a caffeine content of 29-176 mg/cup for brewed and instant coffees. In the USA, mean caffeine contents were 115 mg (range, 60-180 mg)/150-ml cup of drip coffee, 80 mg (40-170 mg) of percolated coffee and 65 mg (30-120 mg) of instant coffee (Lecos, 1984).

Coffee consumption by different populations also varies widely, depending on the type of coffee used and brewing practices. In any single region, coffee brews differ widely in terms of the concentration of soluble solids and chemical constitution, as in urban areas of Scandinavia where boiled, filtered and espresso types are likely to be consumed. Data on consumption of coffee and caffeine are thus available for only a few countries.

(i) *Australia*

Tea consumption is still greater than that of coffee, which is, however, increasing at a rate of approximately 2% per year (94 l per person in 1986). Instant coffee constitutes 85% of total consumption, but brewed coffee usage is increasing slowly. Consumption of decaffeinated coffee is static and contributes only a few percent to the total.

(ii) *Germany (western)*

Coffee is the most popular beverage (170 l per person in 1986), and consumption, which is still increasing (+6% in 1987), is slightly higher than that of fruit juice, mineral water, soft drinks and beer; 90% of the coffee consumed is arabica. Tea consumption is estimated to be 27 l *per caput*. The market shares of various coffee preparations are: brewed coffee, approximately 90%; instant coffee, 10% (down and still decreasing); 'treated' coffees (health coffees), 8.9% (in 1987; decreasing slowly); 'natural mild taste' coffees, 20.8% (in 1987; increasing fast); and decaffeinated coffee, 13.8% (increasing slowly). Approximately 90% of the population drink coffee (*versus* 16% tea and 14% cola drinks), and 80% of it is consumed at home (Hudler, 1988). The number of cups drunk is slowly increasing (4.18 cups per person aged 15 years or more per day in 1987; International Coffee Organization, 1988a).

(iii) *France*

Consumption of coffee is decreasing slightly, while the percentage of arabica coffee compared to robusta consumed is increasing, leading to a decrease in caffeine intake from coffee. Levels of consumption are: brewed coffee, 75%; instant coffee, 15%; coffee-chicory mixtures, 10%; and decaffeinated coffee, approximately 8% of all types drunk. The number of cups consumed per day is 1.47 per person; 80% of the total population drink coffee (44 million persons drinking 1.83 cups per day): 40% of children aged 0-14 years (4.4 million children) drink 0.87 cup per day, and 90% of people aged 15 years or more (39.6 million people) drink 1.88 cups per day (Debry, 1989).

(iv) *Italy*

Consumption of coffee is still increasing slowly. The market shares of the various coffees are: brewed, 95.4% (in 1986); instant, 2.4% (increasing); and decaffeinated, 2.2%. Approximately 70% of coffee is drunk at home (brewed in a 'mocca' machine), 27% in bars (espresso machine) and 3% in vending machines (mostly instant coffee) (Anon., 1988).

(v) *Japan*

Consumption of coffee is increasing rapidly, although it is still much lower than that of tea. In 1983, 83.9% of the population drank coffee (*versus* 93% green

tea, 63% black tea and approximately 50% cola drinks), with instant accounting for 58%, brewed, 32%, and canned, 10%. In 1987, total consumption was 1.38 cups per day (brewed, 0.44; instant, 0.73; canned, 0.19), was higher among men than among women and was highest among people aged 18-39 years (International Coffee Organization, 1988b).

(vi) *Netherlands*

Consumption of coffee is increasing slowly, and per-caput consumption is the highest in Europe outside the northern European countries (Anon., 1987). Practically all of the coffee consumed is brewed, 70% of which is drunk at home (Douwe-Egberts, 1989).

(vii) *Nordic countries* (Denmark, Finland, Iceland, Norway and Sweden) (Kraft General Foods, 1989)

Consumption of brewed coffee is relatively stable (approximately 10 kg *per caput* per year), with small declines in Sweden and Iceland and a marked decline in Denmark. Nearly all of the caffeine consumed is from coffee (Gilbert, 1984). More than 95% of all coffee consumed is brewed arabica, and the rest is instant (ranging from 2% in Finland to 10% in Denmark); hardly any decaffeinated coffee is drunk. Estimated ratios of coffee to water used are 55-65 g/l in Finland, 50-60 g/l in Norway and Sweden, 45-55 g/l in Iceland and 40-50 g/l in Denmark, with extraction yields of soluble coffee solids of 18-25%. Filtration is the most common brewing method, followed by boiling (Table 12).

Table 12. Brewing methods used in Nordic countries

Country	Filtered (%)	Boiled (%)
Norway	65	35
Finland	65	35
Sweden	75	25
Denmark	95	5
Iceland	95	5

(viii) *Switzerland*

Per-caput consumption of coffee is estimated at 2.58 cups per day. It is the most popular beverage, followed by milk, mineral water and soft drinks. Brewed coffee is most commonly drunk, but instant coffee is consumed frequently (Nestlé, 1989).

(ix) *UK*

In 1985, tea (mostly black tea) was still the most popular beverage, accounting for 65% of the total hot drink intake *versus* 26% for coffee, but coffee consumption

is increasing. Instant coffee accounts for 85-90% of total consumption; 70-75% of brewed coffee is filtered, 20% is percolated and 5% is espresso coffee. In one report, decaffeinated coffee accounted for 20% of instant and 9% of brewed coffee and for 6% of retail consumption at home (Anon., 1987).

(x) *USA*

In 1989, 52.5% of the population over 10 years of age drank coffee (40.2% brewed, 15% instant), and 29.4% drank tea and 58.8% drank soft drinks. The number of cups of coffee consumed per person per day was 3.12 in 1962, decreased to 1.67 in 1988 and increased to 1.75 in 1989. Consumption per coffee drinker has been stable since 1985 at 3.34 cups per day, but this value had decreased from 4.17 cups per day in 1962. Consumption of decaffeinated coffee has increased from 4% in 1962 to 16.7% in 1989, at 2.40 cups per drinker per day (International Coffee Organization, 1989f,h).

Trends in coffee consumption over 1957-89 in the USA by type of coffee, region, age group, sex, location and time of day are given in Table 13. Consumption of brewed and instant coffee declined by an average of about 46% between 1962 (the year of highest average consumption) and 1989. The proportion of cups prepared from decaffeinated coffee (ground and soluble) increased from 3% to 19% during 1962-89, and the proportion of the total population drinking coffee has declined sharply, from 74.7% to 52.5% (Gilbert, 1984; International Coffee Organization, 1989f,h). Consumption of decaffeinated coffee in the USA in 1985-88 and in 1962 is given in Table 14 (International Coffee Organization, 1989h), which shows an increase of nearly four times. The decrease in the proportion of the population drinking coffee in 1988 from that in 1985 was seen across all age groups, with a large decrease in drinkers aged 30-59 years. Almost twice as many people aged 30 years and over drink coffee than do those younger than 30.

2. Chemical Composition

2.1 General aspects

Roasted, ground and decaffeinated coffee, in their dry form, consist of a soluble and an insoluble portion; the proportions of each in the beverage depends upon the brewing conditions and the appliance used. While it is possible by exhaustive extraction in the laboratory to obtain 30-32% w/w soluble substances from roasted coffee, the more usual yield in household brews is 15-25% w/w. As mentioned above, the ratio of weight of dry product to volume of water used for brewing also varies according to national and local tastes; variations also occur in

Table 13. Coffee consumption trends in the USA in people aged 10 years and over, 1957–89[a]

	Cups per person per day													Difference 1962–89	Change (%)
	1957	1962	1967	1972	1977	1982	1983	1984	1985	1986	1987	1988	1989		
Type															
Brewed	2.32	2.45	2.19	1.67	1.30	1.33	1.31	1.44	1.39	1.37	1.37	1.31	1.43	−1.02	−42
Instant	0.50	0.67	0.65	0.68	0.64	0.56	0.53	0.54	0.42	0.36	0.37	0.34	0.32	−0.35	−52
Decaffeinated	NA	0.10	0.16	0.17	0.27	0.38	0.39	0.44	0.42	0.41	0.43	0.38	0.40	+0.30	+200
All	2.82	3.12	2.84	2.35	1.94	1.90	1.87	1.99	1.83	1.74	1.76	1.67	1.75	−1.37	−44
Region															
North-east	2.72	2.91	2.63	2.10	1.79	1.85	1.90	1.90	1.84	1.86	1.75	1.58	1.79	−1.12	−38
North-central	2.99	3.34	3.18	2.66	2.34	2.18	2.06	2.27	2.04	1.92	1.90	1.96	1.98	−1.36	−41
South	2.48	2.78	2.39	1.97	1.99	1.68	1.66	1.84	1.57	1.53	1.58	1.45	1.52	−1.26	−45
West	3.25	3.52	3.19	2.74	1.98	1.96	1.86	2.00	2.01	1.70	1.91	1.77	1.81	−1.71	−49
All	2.82	3.12	2.84	2.35	1.94	1.90	1.87	1.99	1.83	1.74	1.76	1.67	1.75	−1.37	−44
Age group															
10–14	0.19	0.18	0.19	0.12	0.07	0.03	0.04	0.04	0.03	0.02	0.03	0.04	0.02	−0.16	−89
15–19	1.11	1.09	0.82	0.55	0.45	0.33	0.26	0.30	0.21	0.16	0.19	0.23	0.20	−0.89	−82
20–24	2.60	2.99	2.22	1.48	1.36	0.92	0.88	0.92	1.00	0.79	0.55	0.63	0.72	−2.27	−76
25–29	3.65	3.88	3.21	2.47	1.89	1.75	1.60	1.64	1.48	1.32	1.39	1.22	1.23	−2.65	−68
30–39	3.67	4.50	3.99	3.51	2.62	2.37	2.39	2.42	2.24	2.11	2.19	1.91	2.03	−2.47	−55
40–49	3.74	4.44	4.48	3.72	3.49	3.11	2.85	3.15	3.02	2.62	2.75	2.57	2.57	−1.79	−40
50–59	3.16	3.83	3.70	3.35	3.22	3.09	3.27	3.33	2.93	2.77	2.95	2.85	2.97	−0.86	−22
60–69	2.75	3.01	3.16	2.85	2.72	2.65	2.49	2.87	2.51	2.70	2.49	2.49	2.64	−0.37	−12
≥70	2.29	2.39	2.50	2.49	2.00	2.03	1.95	2.18	1.87	2.04	1.85	1.83	1.93	−0.46	−19
Sex															
Male	2.91	3.28	2.93	2.48	2.12	2.06	1.90	2.10	1.91	1.80	1.89	1.86	1.85	−1.43	−44
Female	2.73	2.98	2.77	2.23	1.95	1.75	1.81	1.89	1.76	1.68	1.64	1.50	1.66	−1.32	−44

Table 13 (contd)

	Cups per person per day													Difference 1962–89	Change (%)
	1957	1962	1967	1972	1977	1982	1983	1984	1985	1986	1987	1988	1989		
Location															
Home	2.35	2.57	2.29	1.86	1.62	1.36	1.37	1.40	1.29	1.24	1.23	1.19	1.23	-1.34	-52
Work	0.21	0.26	0.30	0.28	0.16	0.38	0.33	0.38	0.35	0.31	0.33	0.32	0.34	+0.08	+131
Eating places	0.26	0.29	0.25	0.21	0.25	0.14	0.13	0.17	0.14	0.14	0.14	0.12	0.18	-0.11	-38
Time of day															
Breakfast	1.14	1.17	1.13	1.00	0.91	0.88	0.89	0.92	0.88	0.84	0.85	0.83	0.90	-0.27	-23
Other meals	0.96	0.98	0.77	0.59	0.46	0.36	0.36	0.35	0.30	0.27	0.30	0.25	0.22	-0.76	-78
Between meals	0.72	0.97	0.94	0.76	0.66	0.66	0.62	0.71	0.65	0.65	0.61	0.59	0.63	-0.34	-35
% of US population drinking coffee	77.3	74.7	71.4	65.0	57.9	56.3	55.2	57.3	54.9	52.4	52.0	50.0	52.5	-22.2	-30
Cups per drinker per day	3.65	4.17	3.98	3.62	3.51	3.38	3.36	3.48	3.33	3.32	3.38	3.34	3.34	-0.83	-20

[a] From Gilbert (1984); International Coffee Organization (1989f,h)
NA, not available

Table 14. Consumption of decaffeinated coffee in the USA in 1985–88 and in 1962[a]

Year	% of US population drinking coffee	No. of cups per day	
		per person	per drinker
1962	4.0	0.10	2.61
1985	17.3	0.42	2.42
1986	17.1	0.41	2.37
1987	17.5	0.43	2.48
1988	15.8	0.38	2.40
% change:			
1962–88	+11.8	+0.28	–0.21
1985–88	–1.5	–0.04	–0.02

[a] Adapted from International Coffee Organization (1989h)

the nature and origin of the coffee, the appliance and the amount of additives (e.g., milk) used subsequently. All of these factors influence the concentration of soluble substances in the resultant brews and their chemical compositions. Generally, 42, 48 and 57 g roasted, ground coffee are used typically per litre of water in the USA, UK and Europe, respectively, and some 150 ml of the water are retained in the spent coffee grounds.

Soluble substances have already been extracted from instant coffee at the point of manufacture. The percentage removed varies according to brand and may be up to 50%, so that more of the normally insoluble substances are rendered soluble at 100°C. About 12 g/l is a typically used average concentration of product in water for UK and US tastes; it is higher and lower in other countries. Clearly, the composition of different instant coffees varies considerably, especially in the relative proportions of the various constituents.

The main component of the beverages consumed is therefore water. Caffeine has particularly important stimulatory properties, but all three preparations contain other nonvolatile soluble compounds. Compounds of known physiological importance in roasted coffee and instant coffee have been reviewed by Viani (1988). Volatile compounds occur in the dry product, and their presence in the brews is again dependent on the amount and type of product and on the brewing conditions: 40-100% is extracted in practice (Pictet, 1987). The content of volatile substances in instant coffees is particularly dependent upon the sophistication of the method for extracting and retaining such substances on drying. The influence of nonvolatile

and volatile components on the flavour of coffee has been described in detail (Clarke, 1986).

Tables 15 and 16 give a broad tabulation of all components of green and roasted arabica and robusta coffees (Clarke, 1987). It should be noted that considerable variation may occur, depending on factors such as the exact source and storage conditions, especially with regard to the concentrations of compounds that occur at low levels, such as aliphatic acids, reducing sugars and free amino acids. The values for polysaccharides, lignin and pectin are considered to be less reliable than others, as they are derived by indirect analysis from data on hydrolysis; however, they are indicative. For roasted coffee, further differences depend on the degree of roasting. Roasted coffee may also contain roasted seeds, tubers and other parts of vegetable plants, such as chicory. Instant coffee may similarly contain the soluble parts of these materials (Clarke & Macrae, 1987a).

Table 15. Composition of green coffee[a]

Component	Typical average content (dry basis, %)	
	Arabica	Robusta
Alkaloids (caffeine)	1.2	2.2
Trigonelline	1.0	0.7
Minerals (as oxide ash)		
41% potassium and 4% phosphorus	4.2	4.4
Acids		
Total chlorogenic	6.5	10.0
Aliphatic	1.0	1.0
Quinic	0.4	0.4
Sugars		
Sucrose	8.0	4.0
Reducing	0.1	0.4
Polysaccharides ('mannan', 'galactan', 'glucan' and 'araban')	45.0	50.0
Lignin	2.0	2.0
Pectins	3.0	3.0
Proteinaceous compounds		
Protein	11.0	11.0
Free amino acids	0.5	0.8
Lipids		
Coffee oil (triglyceride with unsaponifiable fat)	16.0	10.0

[a] From Clarke (1987)

Table 16. Composition of a medium-roasted coffee[a]

Component	Typical average content (dry basis, %)		% extractable with water at 100°C[b]
	Arabica	Robusta	
Alkaloids (caffeine)	1.3	2.4	75–100
Trigonelline (including roasted by-products)	1.0	0.7	85–100
Minerals (as oxide ash)	4.5	4.7	90
Acids			
Residual chlorogenic	2.5	3.8	100
Quinic	0.8	1.0	100
Aliphatic	1.6	1.6	100
Sugars			
Sucrose	0.0	0.0	-
Reducing	0.3	0.3	100
Polysaccharides (unchanged from green)	33	37	10
Lignin	2.0	2.0	0
Pectins	3.0	3.0	-
Proteinaceous compounds			
Protein	10	10	15–20
Free amino acids	0.0	0.0	-
Lipids (coffee oil)	17	11	1
Caramelized or condensation products (e.g., melanoidins) by difference	23	22.5	20–25
Volatile substances other than acids	0.1	0.1	40–80

[a] From Clarke (1987)
[b] From Maier (1981), for normal household brewing

A general and detailed description of all aspects of the chemistry of coffee has been published (Clarke & Macrae, 1985).

2.2 Compounds present in green, roasted, brewed, instant and decaffeinated coffees

The formulae of some of the compounds described below are given in Appendix 1 to this monograph (p. 199).

The quantitative data presented are generally for dry roasted coffee. To calculate representative values for the content in the beverage consumed, an average usage of 10 g roasted coffee per cup of filtered coffee (150 ml), equivalent to 57 g roasted coffee brewed with 1 l of water, can be assumed. Approximately 86% of the water is in the brew and the remainder left with the grounds. At an extraction

yield of 20% total soluble solids, a concentration of 1.3% w/w would therefore be consumed. Assuming 100% extraction of particulate substances, their content in a cup can be estimated by dividing the content in roasted coffee (mg/kg) by 100.

With some filter devices and using finer grinds (as in the UK), smaller quantities of roasted coffee are used, e.g., 48 g/l of water or 8.3 g/cup. Spiller (1984b) assumed 7.5 g/150-ml cup from US experience; however, Clinton (1985) analysed data from 3000 respondents across the USA and found an average strength of 1.38 g coffee solubles per cup, equivalent to only 6.9 g roasted, ground coffee at 20% yield. Weaker coffee was drunk in the west than in the east.

Another form of expression is that 10 g per cup is equivalent to 100 cups/kg roasted, ground coffee, 8.3 g is equivalent to 122 cups/kg and 6.9 g to 147 cups/kg.

Table 16 gave an indication of the percentages of various components that are extracted. The level may be 75-100% for components such as caffeine and chlorogenic and other acids, but is rather less for volatile components.

(*a*) *Nonvolatile substances*

(i) *Caffeine and other purines*

Extensive determinations of caffeine in green coffees have been reported (Macrae, 1985). These indicate an average of 1.2% on a dry basis (commercial range, 0.9-1.4%) for arabica coffee and 2.2% (commercial range, 1.5-2.6%) for robusta coffee. (Analytical methods are reported in the monograph on caffeine.) The content in roasted coffee is usually somewhat higher than in the corresponding green — by up to 10% in darker roasts — due to physical loss in weight of other components; 0-5% of the caffeine is lost by sublimation. Few reliable direct determinations have been made on roasted coffee, but several have been done on brewed coffee (Table 17; Bunker & McWilliams, 1979; Clinton, 1985). Minute amounts of related alkaloids have been identified and quantified in roasted coffee, e.g., theobromine at 0.009-0.037% and theophylline at 0.00-0.013% (Kazi, 1985; Macrae, 1985); traces of paraxanthine, theacrine and liberine have been detected in unripe green coffees (Viani, 1988).

(ii) *Chlorogenic acids and related substances*

A number of different chlorogenic acids are present; the amount of each depends largely on the degree and type of roasting to which the green coffee has been subjected (Clifford, 1985). 5-Caffeoylquinic acid is present in the largest amounts, in both green and roasted coffees. Dicaffeoyl and feruloyl quinic acids are also present, together with the 3- and 4-isomers of monocaffeoylquinic acid. The total percentage of chlorogenic acids in eight commercial roasted coffee samples ranged from 0.2-3.5% (very dark to light roasting) (Trugo, 1984), and that in 19 samples was 1.6-3.8% (Maier, 1987a). On the basis of 10 g coffee per cup of brew

and 85% recovery, this would indicate a level of 15-325 mg/cup (Viani, 1988). Actual data (Clinton, 1985) from the USA give an average value of 190 mg total chlorogenic acids per cup of brewed coffee. Pyrolysis products of chlorogenic acid, in particular quinic acid and caffeic acid (see p. 69), are also found, depending upon the origin and degree of roasting, as are phenols (see p. 76).

Table 17. Caffeine content per cup of brewed coffee

Reference and location	Type of brew	No. of samples	Cup size (ml)	Caffeine (mg/cup)	
				Average	Range
Estimated by the Working Group[a]	10 g/cup				
	Arabica	–	150 ml	–	102–120
	Robusta	–	150 ml	–	187–220
	7 g/cup				
	Arabica	–	150 ml	–	71–84
	Robusta	–	150 ml	–	131–154
Burg (1975)[b] USA	Percolated	2000	150 ml	83	64–124
Gilbert *et al.* (1976)	Percolated	–	150 ml	74	39–168
Canada	Drip	–	150 ml	112	56–176
Bunker & McWilliams (1979)	Percolated	–	150 ml	104	89–122
USA	Drip	–	150 ml	142	137–149
Lecos (1984)	Percolated	–	150 ml	80	40–170
USA	Drip	–	150 ml	115	60–180
Clinton (1985) USA	Percolated/Drip	3000	197 ml	85	–

[a]On the basis of 1.2% caffeine in roasted dry arabica and 2.2% in roasted dry robusta, and range given for 85% and 100% efficiencies of extraction of caffeine
[b]Cited by Roberts & Barone (1983)
–, not given

(iii) *Glycosides*

Atractyligenin (a nor-diterpenoid substance of the (-)-kaurane series) has been found in coffee, both as the free compound and as the aglycone of three glycosides (Mätzel & Maier, 1983). The content of atractyligenin has been estimated at 2.9-11.5 mg/cup of brewed arabica and 0-0.2 mg/cup of brewed robusta (Viani, 1988).

(iv) *Lipids*

Roasted coffee has a very high lipid content — approximately 16% w/w in arabica and 11% in robusta — associated with two diterpenes specific to coffee,

kahweol and cafestol, mostly combined as glycerides. The total diterpene content is typically reported at 1.3% in green arabica (ratio of cafestol:kahweol, 40:60 to 70:30) and at only 0.2% in green robusta (predominately cafestol) (Viani, 1988).

There appears to be little destruction on roasting; but of greater importance is the fact that little of the oil (lipids) and of these terpenes occurs in brewed coffee, e.g., 0.9 mg lipid (coffee oil) per cup and 0.005 mg diterpenes in filter brews, with rather more in espresso brews (40 and 3.2 mg, respectively) (Viani, 1988).

Various sterols (and their esters with fatty acids) and tocopherols are also present in the lipids, but there is no evidence of their presence in brewed coffee. The presence of various alkanoylated 5-hydroxytryptamines (high C_n fatty acids plus 5-hydroxytryptamine) in the wax on the outer surface of green coffee beans has been examined extensively by Folstar (1985); they are present at 500-1000 ppm (mg/kg), but they are partly destroyed on roasting and very little passes into the brew (van der Stegen, 1979).

(v) *Trigonelline and nicotinic acid*

Trigonelline is present typically at 1.1% in dry arabica green coffee (range, 0.6-1.3) and 0.65% in dry robusta green coffee (range, 0.3-0.9) (Macrae, 1985). The amount destroyed during roasting depends on the degree of roast, e.g., an original 1.1% level will decline to around 0.2% in dark roasts (Trugo, 1984), corresponding to 110 and 20 mg/cup assuming 10 g of roasted coffed per cup. An average content of 53 mg/cup has been reported by Clinton (1985) in the USA. Trigonelline is transformed into several volatile products but also into nicotinic acid (niacin; vitamin PP), of which roasted and brewed coffee can be important sources (100-400 mg/kg) (Macrae, 1985). A content of 0.03-0.05 mg nicotinic acid per cup was reported from six samples (Viani, 1988); Macrae (1985) reported 1 mg/cup and 2-3 mg from a dark roast. Residual trigonelline has been reported at a level of 40-55 mg/cup (Viani, 1988).

(vi) *Acids*

The nature and amount of nonvolatile acids in roasted coffee has been examined extensively, since they can contribute significantly to its flavour (Woodman, 1985; Maier, 1987a; van der Stegen & van Duijn, 1987). Apart from residual chlorogenic acids, the main acids present in significant quantities are quinic, malic, citric, lactic, pyruvic, succinic and glycolic acids (Table 18).

The amount of each acid is strongly dependent upon the degree of roasting, sometimes peaking in medium roasts, such as citric acid in Kenya arabica with 'fine' acidity (van der Stegen & Duijn, 1987).

Table 18. Content of selected nonvolatile acids in roasted coffee

Acid	Content (%, dry weight)[a]					
	Arabica (during roasting)[b]		Arabica (4 samples)[c]	Robusta (4 samples)[c]	Commercial (17 samples)[d]	
	Tanzania	Kenya			Average	Range
Citric	0.87 to 0.55	0.70 to 0.18	[0.67]	[0.48]	0.59	0.43–0.70
Malic	0.39 to 0.24	0.30 to 0.19	[0.33]	[0.13]	0.27	0.10–0.39
Lactic	0.08 to 0.10	0.09 to 0.16	–	–	0.10	0.00–0.18
Pyruvic	0.17 to 0.14	0.09 to 0.09	–	–	–	–
Glycolic	–	–	[0.26]	[0.19]	0.26	0.17–0.49
Succinic	–	–	–	–	0.40	0.19–0.80
Quinic	–	0.56 to 0.87	[0.96]	[1.15]	1.04	0.89–1.50

[a]To convert to milligrams per kilogram, multiply by 10 000; to convert to milligrams per cup multiply by 100.

[b]From Blanc (1977); in samples roasted in the laboratory, with 9–20% loss (i.e., from very light to dark)

[c]From Maier (1987a); in samples roasted in the laboratory, with 17% loss for arabica and 19% for robusta (medium to dark roast); graphic data in millimoles per kilogram, converted by the Working Group

[d]From van der Stegen & van Duijn (1987)

Maier (1987a) also found phosphoric acid [estimated from a graph by the Working Group at 0.19%] in roasted arabica and [0.29%] in roasted robusta; he also found significant amounts of an unspecified high-molecular-weight acid. Other acids have been identified (Spiller, 1984b) but in minor quantities. Maier (1987a) quantified these as citraconic at 0.048-0.070%, 2-furoic at 0.009-0.0250%, itaconic at 0.013-0.020%, pyrrolidone carboxylic (pyroglutamic acid) at 0.06-0.10%, mesaconic at 0.005-0.013%, fumaric at 0.010-0.016% and maleic at 0.006-0.016%; a number of others were found at even lower levels, all in commercial roasted coffees. Tressl *et al.* (1978a) reported 2-furoic acid at 0.008% in an arabica roasted coffee.

The total content of major nonvolatile acids estimated by the Working Group from the data of van der Stegen and van Duijn (1987) is 276 mg/cup (assuming use of 10 g roasted coffee per cup), ranging from 246 to 300; the content estimated from the data of Maier (1987a), including phosphoric acid, averages 231 mg in arabica and 224 mg in robusta. These figures are somewhat higher than the average of 178 mg, including formic/acetic acids, given by Clinton (1985) on the basis of use of 7 g/cup.

Maier (1987a) regarded the combination of citric and acetic acids as the reason for the higher acidity of arabica than robusta coffee. Also significant for flavour is the relatively high amount of quinic acid lactone, which, like quinic acid itself,

increases and decreases again with increasing severity of roasting, peaking at 0.7% on a dry basis (Clifford, 1985). Brews containing this compound and standing at elevated temperatures show increasing acidity, partly because this lactone is transformed into more quinic acid but also because the concentrations of some other acids increase (van der Stegen & van Duijn, 1987).

(vii) *Maillard reaction products (melanoidins)*

Products of the Maillard reaction are important constituents of roasted coffee; in a dry medium roast, they can comprise some 15-20%, of which 20-25% are hot water-soluble. At present, they are poorly characterized as caramelized products of sucrose and condensation products of polysaccharides with 'proteins' and other compounds (Trugo, 1985).

(viii) *Other compounds*

Clinton (1985) found reducing sugars at an average content per cup of 15 mg, other carbohydrates at 205 mg and peptides/'protein' at 62 mg.

(*b*) *Volatile substances*

The volatile compounds in coffee include carbonyl compounds, alcohols, acids, esters, terpenoid compounds, nitrogen- and sulfur-containing compounds, hydrocarbons, heterocyclic and aromatic compounds. The quantity (apart from the volatile aliphatic acids) obtained by distillation of roasted coffee is about 0.1% or 1000 mg/kg (Silwar *et al.*, 1986a). Volatile compounds are present in smaller amounts than in most other foods, but the range of types is greater.

The number of volatile components that have been identified has risen sharply over the last 20 years (Flament, 1987). The most up-to-date, complete listing of all identified components is that of Maarse and Visscher (1986) — now comprising over 700. An earlier listing by Vitzthum (1976) gave 550 volatile compounds (an English version is provided by Spiller, 1984a). Listings by Silwar *et al.* (1986a) and Flament (1987) give numbers only for categories of compounds. The systems of chemical grouping used differ somewhat in these lists, particularly with regard to sulfur-containing and furan-based compounds. The numbers of volatile compounds identified in roasted coffee are listed by group in Tables 19-22.

Those compounds that have been quantified have been listed by van Straten *et al.* (1983) and Silwar *et al.* (1986a,b). Only those detected by modern gas chromatography (GC)/mass spectrometry methods (i.e., published since about 1970) can be regarded as reliably identified, however. Contents are usefully given per cup of brew (standardized at 150 ml) or per litre, and suitable bases for calculation were given above.

Table 19. Classification of volatile compounds in roasted coffee: aliphatic benzenoid and alicyclic compounds[a]

Group/subgroup	Number identified			
	Total	Aliphatic	Benzenoid	Alicyclic
Hydrocarbons	73			
Saturated		24	9	1
Unsaturated		16	2 (in side chain)	1
Condensed polynuclear		–	20	–
Alcohols	20			
Saturated		12	2	1
Unsaturated		4	0	1
Aldehydes	29			
Saturated		11	5	0
Unsaturated		7	1	0
Hydroxy-		0	4	0
Alkoxy-		0	1	0
Ketones	69			
Mono-				
Saturated		23	2	2
Unsaturated		5	0	8
Hydroxy		6	3	0
Acyl-		0	0	1
Di-				
Saturated		13	1	5
Unsaturated		0	0	0
Acids	22			
Saturated		15	1	2
Unsaturated		4	0	0
Esters	29	23	6	0
Ethers	2	2	0	0
Acetal	1	1	0	0
Nitrogen-containing	21			
Amines		12	5	0
Nitriles		3	0	0
Oxime		1	0	0
Sulfur-containing	18			
Thiols		3	0	0
Thioethers (sulfides)				
Mono-		2	1	0
Di-		3	0	0
Tri-		2	0	0

Table 19 (contd)

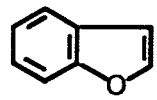
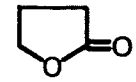
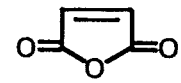
Group/subgroup	Number identified			
	Total	Aliphatic	Benzenoid	Alicyclic
Sulfur-containing (contd)				
Thioester		1	0	0
Thioketone		1	0	0
Thiophenol		–	1	–
Miscellaneous (CS_2 etc.)		4	0	0
Phenols	40			
Mono-			1	
Alkylated		–	22	–
Alkoxy-		–	8	–
Dihydroxy benzenes		–	7	–
Trihydroxy benzenes		–	2	–
Total	324	198	104	22

[a]From Maarse & Visscher (1986)
–, not applicable

Silwar *et al.* (1986a,b) stated that steam distillation of a medium-roasted arabica coffee released 700-800 ppm (mg/kg) by weight of 'aromatics', which corresponds to the 0.1% generally previously believed to be present, if acetic and formic acids are excluded. By GC analysis, they were able to account for 85-95% of this amount by summation of individually determined amounts: 170 compounds were found in the parts per million (milligrams per kilogram) range (1-150 ppm) and 70 in the parts per billion range (1-500 ppb); however, actual data were given for only 157 compounds. The greatest amount of the steam volatile complex by weight was contributed by heterocyclic compounds (80-85%), comprising furans of all kinds (at 38-45%), pyrazines (25-30%), pyridines (3-7%), pyrroles (2-3%), sulfur-substituted furans (0.4%), thiophenes (0.4%), thiazoles (0.15%) and oxazoles (<0.01%). Only 3-5% by weight were aliphatic compounds, 3-5% were aromatic compounds and <0.5% were alicyclic compounds.

A compilation of the data of Silwar *et al.* (1986a,b) is given in Table 23 to illustrate the expected content of volatile compounds per cup of brewed coffee. It is assumed that the extraction efficiency of home brewing is 100%, although in practice it is substantially less. Maarse and Visschler (1986) identified 715 compounds (see Tables 19-22).

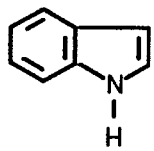
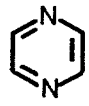
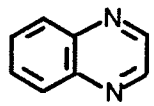
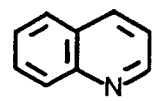
Table 20. Classification of volatile compounds in roasted coffee: heterocyclic (oxygen ring-containing compounds)[a]

Group/subgroup	Number identified						
	Total	Furans	Benzo-furans	Pyrones	Pyrans	Lactones (maleic)	Anhydrides
							
Simple	5	1	1	0	0	3	0
Hydrogenated	8	5	1	0	2	0	0
Alkyl-	42	29	1	3	0	6	3
Alkoxy-	1	1	0	0	0	–	–
Aryl-	1	1	0	0	0	–	–
Difuryl	8	8	0	–	–	–	–
Aldehydes	6	6	0	–	–	–	–
Ketones (including hydrogenated)	15						
Mono-		10	0	–	–	–	–
Di-		5	0	–	–	–	–
Acyl-	9	9	0	–	–	–	–
Alcohols	2	2	0	–	–	–	–
Acid	1	1	0	–	–	–	–
Esters	11	11	0	–	–	–	–
Ethers	4	4	0	–	–	–	–
Sulfur-containing	18						
Thiols		2	0	–	–	–	–
Thioethers		14	0	–	–	–	–
Thioester		1	0	–	–	–	–
Thioketone		1	0	–	–	–	–
Total	131	111	3	3	2	9	3

[a]From Maarse & Visscher (1986)

–, not applicable

Table 21. Classification of volatile compounds in roasted coffee: heterocyclic (nitrogen ring-containing compounds)[a]

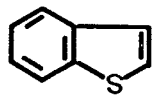
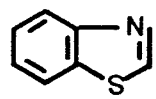
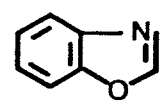
Group/subgroup	Number identified						
	Total	Pyrroles	Benzo-pyrroles (indoles)	Pyra-zines	Benzo[*a*]-pyrazines (quinoxa-lines)	Pyri-dines	Benzo[*b*]-pyridines (quinolines)
							
Simple	6	1	1	1	1	1	1
Hydrogenated	9	2	1	0	5	1	0
Alkyl-	77	28	2	34	4	6	3
Furfuryl-	27	14	0	13	0	0	0
Aryl-	1	1	0	0	0	0	0
Acyl-	30	20	0	7	0	3	0
Alkoxy-	4	0	0	4	0	0	0
Ketones (mono- and di-)	3	2	1	0	0	0	0
Alicyclic	12	0	0	12	0	0	0
Other	2	0	0	0	1	1	0
Total	171	68	5	71	11	12	4

[a]From Maarse & Visscher (1986)

(i) *Carbonyl compounds* (Table 24)

Maarse and Visscher (1986) listed 18 aliphatic aldehydes in freshly roasted coffee, in a saturated series up to heptanal, including seven unsaturated but no alicyclic compounds. *trans*-2-Nonenal is believed to be present in a very small amount. Glyoxal, methylglyoxal and ethylglyoxal are not listed as being present in roasted coffee by Maarse and Visscher (1986) and were not quantified by Silwar *et al.* (1986a) using a direct, non-derivative GC method; however, methylglyoxal has been detected by indirect GC methods (Kasai *et al.*, 1982; Hayashi & Shibamoto, 1985; Nagao *et al.*, 1986a; Shane *et al.*, 1988; Aeschbacher *et al.*, 1989) (Table 25; see also the monograph on methylglyoxal, p. 446).

Table 22. Classification of volatile compounds in roasted coffee: heterocyclic (sulfur, sulfur/nitrogen and nitrogen/oxygen ring–containing compounds)[a]

Group/subgroup	Number identified						
	Total	Thiophenes 	Benzothiophenes 	Thiazoles 	Benzothiazoles 	Oxazoles 	Benzoxazoles 
Simple	4	1	1	1	1	0	0
Hydrogenated	1	0	0	0	0	1	0
Alkyl-	56	7	0	23	0	20	5
Di-		1	0	0	0	0	0
Aryl-	2	1	0	0	0	1	0
Ketones	5	5	0	0	0	0	0
Acyl-	13	9	0	2	0	2	0
Alcohols	1	1	0	0	0	0	0
Esters	3	3	0	0	0	0	0
Other	4	4	0	0	0	0	0
Total	89	32	1	26	1	24	5

[a] From Maarse & Visscher (1986)

Table 23. Volatile compounds in coffee brewed from 10 g medium-roasted arabica coffee[a]

Group	Number identified	Number quantified	Total (mg/cup)[b]
Carbonyls	≥97 26 furanoid	≥12 18 furanoid	0.10–0.20 1.30–1.91
Volatile acids	≥21 1 furanoid	≥ 2 1 furanoid	65 (mainly acetic acid)
Alcohols	≥20 2 furanoid	≥ 5 2 furanoid	0.9–1.35 (mainly furfuryl alcohol)
Esters, lactones and ethers	≥40 15 furanoid	≥ 0 7 furanoid	< 0.07
Pyrroles	≥66 4 indoles	≥14 2 indoles	0.13–0.16
Pyrazines	71	28	1.7–2.2
Pyridines	10	2	
Furans (not already included)	45	21	< 0.04
Phenols and phenol ethers	40	9	0.12–0.29

Table 23 (contd)

Group	Number identified	Number quantified	Total (mg/cup)[b]
Sulfur compounds	95	21	0.1
Others	139	14	Very small
Total	≥692	158	< 4.46–6.11 (excluding acids)

[a] Adapted from Silwar *et al.* (1986a,b)
[b] Calculated by the Working Group

Table 24. Contents of carbonyls in roasted coffee (mg/kg)

Compound	Content[a] (ppm; mg/kg)	Reference
Aldehydes		
Aliphatic		
3-Methyl butanal	6.7	van Straten *et al.* (1983)
n-Hexanal	0.3–0.7	Silwar (1982)
Benzenoid		
Benzaldehyde	1.8, 0.7–1.10	Silwar (1982); Silwar *et al.* (1986a)
3,4-Dihydroxybenzaldehyde	8–20	Tressl *et al.* (1978a)
4-Hydroxy-3-methoxybenzaldehyde (vanillin)	2–3	Tressl *et al.* (1978a)
3,4-Dihydroxycinnamaldehyde	5–12	Tressl *et al.* (1978a)
2-Phenylbut-2-enal	0.6, 0.1–0.20	Silwar (1982); Silwar *et al.* (1986a)
2-Phenylacetaldehyde	3.7, 1.5–2.0	Silwar (1982); Silwar *et al.* (1986a)
Furanoid		
Furfural	5.2–232, 55–80	Silwar (1982); Silwar *et al.* (1986a)
5-Methylfurfural	216, 50–70	Silwar (1982); Silwar *et al.* (1986a)
5-(Hydroxymethyl)-2-furfural	10–35	Tressl *et al.* (1978a)
(2-Furyl)acetaldehyde	0.5	Silwar (1982)
Ketones and diketones		
Aliphatic		
1-Hydroxypropan-2-one	4, 0.25–0.30	Silwar (1982); Silwar *et al.* (1986a)
3-Hydroxybutan-2-one	4.9, 0.25–0.35	Silwar *et al.* (1986a)
2,3-Butanedione (diacetyl)	2.7, 0.05–0.15	Silwar *et al.* (1986a)
2-Pentanone	0.4–4.3	Silwar (1982)
4-Methylpentan-2-one	6.5	Silwar (1982)
2-Hydroxypentan-3-one	5.2, 0.05–0.15	Silwar (1982); Silwar *et al.* (1986a)

Table 24 (contd)

Compound	Content[a] (ppm; mg/kg)	Reference
Ketones and diketones (contd)		
Aliphatic (contd)		
2,3-Pentanedione	1.0–3.0	Silwar *et al.* (1986a)
5-Methylhexan-2-one	0.5	Silwar (1982)
2,3-Hexanedione	3.2, 0.3–0.5	Silwar (1982); Silwar *et al.* (1986a)
3-Heptanone	0.4	Silwar (1982)
4-Heptanone	0.5	Silwar (1982)
2-Pentadecanone	2.9, 0.10–0.15	Silwar (1982); Silwar *et al.* (1986a)
1-Acetoxy-2-propanone	2.0–5.0	Silwar *et al.* (1986a)
1-Acetoxy-3-butanone	2.0–4.0	Silwar *et al.* (1986a)
1-Acetoxy-2-butanone	2.0–3.0	Silwar *et al.* (1986a)
Benzenoid		
2-Hydroxyacetophenone	1.6	Silwar (1982)
Alicyclic		
3-Methylcyclopentane-1,2 dione (3-Methyl-2-hydroxycyclo-pent-2-ene-1-one) (cyclotene)	17–40	Tressl *et al.* (1978a)
Furanoid		
2-Methyltetrahydrofuran-3-one	10.0–16.0	Silwar *et al.* (1986a)
2,4-Dimethyl-2*H*-furan-3-one	0.50–0.60	Silwar *et al.* (1986a)
2,5-Dimethyl-2*H*-furan-3-one	10.7	Silwar (1982)
2,5-Dimethyl-4-hydroxy-2*H*-furan-3-one (furaneol)	25–50	Tressl *et al.* (1978a)
2,5-Dimethyl-4-ethoxy-2H-furan-3-one	2–8	Tressl *et al.* (1978a)
2-Acetylfuran	24.1–31.4	Silwar (1982)
	6.0–12.00	Silwar *et al.* (1986a)
2-Acetonylfuran	2.2	Silwar (1982)
2-Propionylfuran	0.5, 1.10–1.50	Silwar (1982); Silwar *et al.* (1986a)
1-(2-Furyl)butan-2-one	1.4, 0.10–0.20	Silwar (1982); Silwar *et al.* (1986a)
4-(2-Furyl)butan-2-one	4.6, 0.10–0.15	Silwar (1982); Silwar *et al.* (1986a)
1-(5-Methyl-2-furyl)butan-2-one	0.8, 0.25–0.35	Silwar (1982); Silwar *et al.* (1986a)
4-(5-Methyl-2-furyl)butan-2-one	0.25–0.30	Silwar *et al.* (1986a)
1-(2-Furyl)pentan-1,2-dione	1.0, 0.05–0.10	Silwar (1982); Silwar *et al.* (1986a)
2-Acetyl-5-methylfuran	0.5–1.0	Silwar *et al.* (1986a)
2-Methyl-5-propionylfuran	4.2	Silwar (1982)
1-(2-Furyl)-propane-1,2-dione	3.9, 0.10–0.15	Silwar (1982); Silwar *et al.* (1986a)
1-(5-Methyl-2-furyl)propane-1,2-dione	3.4, 0.25–0.30	Silwar (1982); Silwar *et al.* (1986a)

Table 24 (contd)

Compound	Content[a] (ppm; mg/kg)	Reference
Ketones and diketones (contd)		
Furanoid (contd)		
1-(2-Furyl)butane-1,2-dione	3.3, 0.10–0.15	Silwar (1982); Silwar *et al.* (1986a)
1-(5-Methyl-2-furyl)butane-1,2-dione	1.4, 0.05–0.10	Silwar (1982); Silwar *et al.* (1986a)

[a] One figure is given for one sample; Silwar *et al.* (1986a) tested five commercial samples of roasted arabica coffee, while Silwar (1982) and Tressl *et al.* (1978a) tested numerous samples of arabica and robusta coffee.

Table 25. Contents of methylglyoxal in coffee

Content			Reference
Roasted coffee (mg/kg)	Brewed coffee		
	Amount	Conditions	
[58–75]	470–730 µg/cup	8 g/100 ml	Kasai *et al.* (1982)
25	76 µg	3 g/180 ml	Hayashi & Shibamoto (1985)
–	7 µg/ml	10 g/150 ml	Nagao *et al.* (1986a)
–	273–341 µg/g (filtered coffee)	25 g/250 ml	Shane *et al.* (1988)
[21–39][a]	106–197 µg/g dried product	1 g/10 ml	Aeschbacher *et al.* (1989)

[a] Calculated assuming extraction yield of 20% dry soluble solids in the brew

van Straten *et al.* (1983) reported quantitative data on only two of the 18 aldehydes. While acetaldehyde has been reported repeatedly as being present, no reliable quantitative data appear to be available. Hayashi *et al.* (1986) reported a level of 3.4-4.5 ppm (mg/l) formaldehyde (see IARC, 1982, 1987) in brewed coffee.

Maarse and Visscher (1986) listed 11 benzenoid aldehydes; van Straten *et al.* (1983) reported quantitative data on five of them, including 3,4-dihydroxybenzaldehyde at 8-20 ppm (mg/kg) and benzaldehyde at 1.8 ppm (mg/kg). The later work of Silwar *et al.* (1986a), which was not in this listing, generally reported lower levels of all carbonyls quantified in a medium-roasted arabica coffee and a lower level of benzaldehyde, and included 2-phenylacetaldehyde (1.5-2 mg/kg).

Other important aldehydes present are furanoid (six quantified by van Straten *et al.*, 1983); in particular, furfural has been found at up to 255 ppm (mg/kg)

[equivalent to 2.6 mg/cup] and 5-methylfurfural at up to 216 ppm (mg/kg; Silwar, 1982). However, Silwar *et al.* (1986a) reported much lower quantities (up to 80 and 70 ppm (mg/kg), respectively).

Maarse and Visscher (1986) list 47 aliphatic and 16 alicyclic ketones, including diketones, three acetophenones, two benzenoid ketones and one benzenoid diketone. van Straten *et al.* (1983) reported quantitative data on 14 of these, although only 3-methylcyclopentane-1,2-dione (cyclotene) is present at significant amounts of 17-40 ppm (mg/kg; Tressl *et al.* (1978a). This compound was not reported by Silwar *et al.* (1986a). Diacetyl (2,3-butadione) was present at 2.7 ppm (mg/kg; Silwar, 1982), but Silwar *et al.* (1986a) reported only 0.05-0.15 ppm (mg/kg) diacetyl [equivalent to 0.5-15 μg/cup]. They also gave data on 10 aliphatic ketones, three benzenoid aldehydes and 14 furanoid ketones.

Strictly speaking, a number of other pyrrole-based carbonyls could be included; but these are described with nitrogen compounds, and the quantities involved are small. Isomaltol (2-acetyl-3-hydroxyfuran) has been found in arabica and robusta coffees at levels of 8 and 1.5 ppm (mg/kg), respectively (Tressl *et al.*, 1978a).

(ii) *Alcohols*

Maarse and Visscher (1986) listed 18 basic aliphatic and alicyclic alcohols and two aromatic alcohols; van Straten *et al.* (1983) quoted quantitative amounts for only four of them.

Furfuryl alcohol (grouped by Maarse & Visscher (1986) in the furan group) is the most prevalent volatile compound in roasted coffee (except acetic acid), with reported levels of 300 ppm (mg/kg) in arabica and 520 ppm (mg/kg) in robusta (Tressl *et al.*, 1978a), up to 881 ppm (mg/kg; van Straten *et al.*, 1983) and 678 ppm (mg/kg; Silwar, 1982). 5-Methylfurfuryl alcohol was reported at 25 ppm (mg/kg; Silwar, 1982). Silwar *et al.* (1986a) later reported levels of 90-135 ppm (mg/kg) furfuryl alcohol and 1.2-1.8 ppm (mg/kg) 5-methylfurfuryl alcohol. Furfuryl alcohol is regarded as detrimental to the flavour of coffee.

(iii) *Acids*

Maarse and Visscher (1986) listed 19 volatile acids in an aliphatic series up to decanoic, one benzoic and two alicyclic. The quantitative data quoted by van Straten *et al.* (1983) are derived from Kung *et al.* (1967), but the later data of Blanc (1977), Maier (1987a) and van der Stegen and van Duijn (1987) are more reliable (Table 26). The total content of formic and acetic acids found by van der Stegen and van Duijn (1987) would be 6500 ppm [which amount to about 65 mg per cup].

Table 26. Volatile acid content of dry roasted coffees

Coffee	Content (%)		Reference
	Formic acid	Acetic acid	
Colombian and Santos robusta	0.066–0.140	0.25–0.33	Kung *et al.* (1967)
Kenya arabica (very dark to very light)	–	0.4–0.09	Blanc (1977)
Arabica (average of 4 samples, peak value)[a]	0.23	0.60	Maier (1987a)
Robusta medium roast (average of 4 samples)[a]	0.23	0.54	Maier (1987a)
17 commercial coffees (average and range)	0.22 (0.18–0.25)	0.43 (0.36–0.55)	van der Stegen & van Duijn (1987)

[a]Calculated by the Working Group
–, not tested

Kung *et al.* (1967) reported the presence of nine other acids in relatively low quantities. Silwar *et al.* (1986a) gave levels only for 2-methylbutanoic acid, at 25.0-40.0 ppm (mg/kg).

(iv) *Esters, ethers and lactones*

Maarse and Visscher (1986) reported the presence of 23 aliphatic, six benzenoid esters and 11 furanoid-based esters. None of these is reported to be present in any substantial amount; methyl salicylate is reported at 1.4 ppm (mg/kg) and furfuryl acetate at 16.3 ppm (mg/kg; Silwar, 1982) or 3.5-5.5 ppm (mg/kg; Silwar *et al.*, 1986a), but there are few other quantitative data. Six ethers and nine lactones are listed by Maarse and Visscher (1986), and are reported in relatively small amounts by Silwar *et al.* (1986a).

(v) *Nitrogen compounds*

Amines and amides: Maarse and Visscher (1986) listed the presence of 12 aliphatic amines; van Straten *et al.* (1983) reported quantitatively only on dimethylamine at 2 ppm (mg/kg) and on five aromatic amines. One imide, *N*-α-dimethylsuccinimide (Maarse & Visscher, 1986), and the secondary amine, pyrrolidine (Singer & Lijinsky, 1976), have been reported.

N-N/S- *and* N/O-*Heterocyclic compounds*: This is an important group of compounds with regard to the flavour of roasted coffee. Maarse and Visscher (1986) listed the presence of 71 pyrazines, 12 pyridines, four quinolines, 11 quinoxalines, 26 thiazoles, 24 oxazoles, 68 pyrroles and five indoles.

A considerable amount of quantitative data was reported by Tressl *et al.* (1981) and van Straten *et al.* (1983) on 44 of the pyrroles and 25 of the pyrazines. The

quantities of individual pyrroles are quite low (in general < 1 ppm), although levels of 1.1-2.7 ppm (mg/kg) pyrrole itself and 17 ppm (mg/kg) 2-formyl-1-methylpyrrole were reported. Some pyrazines occur at higher levels (104 ppm (mg/kg) methyl pyrazine), but most are found at lower levels (acetyl pyrazine, 1.3 ppm (mg/kg)). Pyridine was reported to be present at up to 49 ppm (mg/kg; van Straten *et al.*, 1983). Quantitative data on 18 pyrroles (including 13 carbonylic) give a total of 79 ppm (mg/kg); 2 ppm (mg/kg) were found for two indoles and 395 ppm for 28 pyrazines (Silwar, 1982). Silwar *et al.* (1986a) provided quantitative data on 28 pyrazines (170-218 mg/kg), two pyridines, 14 pyrroles (mainly carbonylic, 12.6-15.0 mg/kg) and two indoles.

2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ) (see IARC, 1986b) has been detected in coffee beans at 16 ng/kg (hot-air-roasted), 32 ng/kg (charcoal-roasted) and 150 ng/kg (high-temperature-roasted) only after alkaline hydrolysis (Kikugawa *et al.*, 1989; Takahashi *et al.*, 1989).

S- *and* O/S-*Heterocyclic compounds*: Maarse and Visscher (1986) reported the presence of 28 thiophenes and two dithiolanes and provided some quantitative data; none occurs in apparently significant amounts. Silwar (1982) found six thiophenes at a total content of 8.9 ppm (mg/kg) and one dithiolane at 3.7 ppm (mg/kg). Silwar *et al.* (1986b) reported the total content of six thiophenes at 4.7 ppm (mg/kg) in roasted Colombian arabica and 3.2 in roasted robusta coffee.

(vi) *Furan-based compounds*

Maarse and Visscher (1986) reported the presence of 92 furan compounds and a further 18 sulfur-containing furan compounds, many of which have been mentioned previously (as aldehydes, ketones and esters). Furfurylthiols (furfuryl mercaptans) and sulfides appear to be especially important with regard to flavour but are present in only small absolute quantities, e.g., furfurylthiol at 2.2 ppm (mg/kg) in roasted robusta, at 1.1 ppm (mg/kg) in arabica (Tressl & Silwar, 1981), at 1.65 ppm (mg/kg) in roasted Ivory Coast robusta and at 0.9 ppm (mg/kg) in roasted Colombias (Silwar *et al.*, 1986b). The total content of ten sulfur-containing furans was only 2.5-6.4 ppm (mg/kg; van Straten *et al.*, 1983). The total content of 17 furans was 41 ppm (mg/kg), with 2-acetylfuran contributing 31.4 ppm (Silwar, 1982; van Straten *et al.*, 1983). Kahweofuran (2-methyl-3-oxa-8-thiabicyclo(3.3.0)-1,4-octadiene), of particular importance in flavour, has been reported at 1.75 ppm (mg/kg) in roasted Colombian arabicas, at 2.0 ppm (mg/kg) in Kenyan coffees and at 0.45 ppm (mg/kg) in roasted Ivory Coast robustas (Silwar *et al.*, 1986b).

(vii) *Other sulfur compounds*

A number of other aliphatic and aromatic sulfides, including di- and trisulfides, are especially important in the aroma of dry roasted coffee. Maarse and

Visscher (1986) listed 14 aliphatic and two aromatic sulfides. The quantities involved are very small; e.g., dimethyldisulfide was found at 0.01 ppm (mg/kg) in roasted Colombian arabica and at 0.1 ppm in roasted Ivory Coast robustas (Tressl & Silwar, 1981; Silwar *et al.*, 1986b).

(viii) *Phenols*

Phenols are another important group of flavour compounds; 39 were listed by van Straten *et al.* (1983). Quantitative determinations were reported by Tressl (1977), Tressl *et al.* (1978a,b), van Straten *et al.* (1983) and Silwar *et al.* (1986a). Silwar *et al.* (1986a) reported on the contents of 13 phenols (excluding dihydroxy- and trihydroxybenzenes) in a medium-roasted arabica. The actual quantities present are again small; the differences between roasted robusta and arabica are shown in Table 27. When arabica coffee is roasted very darkly, greater quantities of some phenols have been found, e.g., the phenol content increased from 13 to 63 ppm (mg/kg) and that of guaiacol from 2.7 to 10.6 ppm (Tressl *et al.*, 1978b).

(ix) *Pyrones*

Three pyrones have been identified and quantified by Tressl *et al.* (1978a) and reported by van Straten *et al.* (1983; Table 28).

(x) *Hydrocarbons*

Seventy-three hydrocarbons have been identified in roasted coffee (Maarse & Visscher, 1986); 11 have been quantified at the parts per billion (micrograms/kilogram) level and four at the parts per million (milligrams/kilogram) level (van Straten *et al.*, 1983).

As both roasted and instant coffee are derived by roasting procedures (at temperatures of the order of 210°C, with higher air temperatures), polycyclic aromatic hydrocarbons (PAH), and in particular benzo[*a*]pyrene, can be expected to be present. Numerous studies have been conducted on their actual occurrence (e.g., Ruschenburg, 1985; de Kruijf *et al.*, 1987; reviewed by Strobel, 1988a). Determinations in roasted coffee, best done by high-performance liquid chromatography (HPLC) and fluorimetric techniques, suggest a range of <0.1-1.2 µg/kg, with an average of 0.3 µg/kg; however, PAH are largely removed in the spent grounds (e.g., on filter papers), leading to contents in the brews of <0.01 µg/l (Ruschenburg, 1985) or 0.0003-0.0008 µg/l (de Kruijf *et al.*, 1987). Darker roasts produce slightly higher values. It has been shown that the chaff produced during roasting contains much higher levels (2-23 µg/kg) (de Kruijf *et al.*, 1987); although this material is usually discarded, it is sometimes mixed in with subsequently ground roasted coffee. Strobel (1988a) calculated that coffee consumption contributes <0.1% (or 0.25 µg per year per person) of the total PAH inhaled or ingested from all sources.

Table 27. Phenol content of roasted coffees[a]

Phenolic compound	Content (mg/kg)		
	Arabica	Robusta	Not stated
Phenol	13, 1.20–2.20[b]	17	60
2-Methylphenol (*ortho*-cresol)	1.2, 0.70–1.10[b]	1.1	12.4
3-Methylphenol (*meta*-cresol)	0.7, 0.15–0.50[b]	1.2	7.4
4-Methylphenol (*para*-cresol)	1.3, 0.30–0.60[b]	1.0	13.2
2-Ethylphenol			1.7
3-Ethylphenol			1.3
4-Vinylphenol	0.2	0.2	0.6
2,3-Dimethylphenol			2.1
2,4-Dimethylphenol			2.0
2,5-Dimethylphenol			1.5
2,6-Dimethylphenol			0.2
3,4-Dimethylphenol			0.8
2-Ethyl-4-methylphenol			1.0
4-Ethyl-2-methylphenol			0.9
Ethylmethylphenol			0.4
2-Propyl-4-methylphenol			0.2
Methylpropylphenol			0.2
2,3,5-Trimethylphenol			0.3
2,4,5-Trimethylphenol			0.3
2,3,6-Trimethylphenol			0.2
1,2-Dihydroxybenzene (pyrocatechol)	80	120	
1,4-Dihydroxybenzene (hydroquinone)	40	30	
1,2-Dihydroxy-3-methylbenzene		9[c]	
1,2-Dihydroxy-4-methylbenzene	16	13	
1,2-Dihydroxy-4-ethylbenzene	37	80	
1,2-Dihydroxy-4-vinylbenzene	25	25	
2-Methoxyphenol (guaiacol)	2.7, 2–3[b]	8.4	10.6
4-Methyl-2-methoxyphenol	0.01–0.02[b]		0.1
4-Ethyl-2-methoxyphenol	0.8–1.50[b]		2.2
4-Vinyl-2-methoxyphenol	9.5, 8–20.0[b]	19.5	7.9
4-Propenyl-2-methoxyphenol (isoeugenol)			0.1
1,2-Dimethoxy-4-vinylbenzene	0.40–0.80[b]		3[d]
1,2,4-Trihydroxybenzene	20	13	
1,2,3-Trihydroxybenzene (pyrogallol)	45	55	

[a] Data from Tressl *et al.* (1978a,b) unless noted otherwise
[b] From Silwar *et al.* (1986a)
[c] From van Straten *et al.* (1983)
[d] From Silwar (1982)

Table 28. Pyrone content of roasted coffees[a]

Pyrone	Content (mg/kg)	
	Arabica	Robusta
3-Hydroxy-2-methyl-4-pyrone (maltol)	39	45
5,6-Dihydro-3,5-dihydroxy-2-methyl-4-pyrone (or 5,6-dihydro-5-hydroxymaltol)	13	10
3,5-Dihydroxy-2-methyl-4-pyrone (5-hydroxymaltol)	15	6

[a] From Tressl *et al.* (1978a)

(xi) *Other compounds*

Hydrogen peroxide has been found in roasted coffee (Fujita *et al.*, 1985a).

(c) *Compounds in instant coffee*

The quantitative data presented refer generally to dry instant coffee (powder or granules). To obtain representative values for the content in the beverage, it is convenient and realistic to assume use of 2 g instant coffee per 150-ml cup. With 100% solubility, the content in milligrams per kilogram for a given component of instant coffee should be divided by 500 to give the content in milligrams per cup.

(i) *Nonvolatile substances*

Caffeine and other purines: Caffeine levels have been determined directly in 12 commercial samples using HPLC methods (Trugo *et al.*, 1983); the range was 28-48 g/kg [which would correspond to 56-92 mg/cup]. The higher level resulted from higher levels of robusta in the blend. The caffeine contents of instant coffees manufactured in Brazil are somewhat lower: Angelucci *et al.* (1973), using a spectrophotometric method on 15 arabica samples, reported levels of 1.63-3.86%, with one robusta containing 4.64%. Minute amounts of the other alkaloids that occur in roasted and green coffees also appear in instant coffee, at approximately half the amount.

Chlorogenic acids and related substances: Trugo and Macrae (1984b) determined by HPLC the chlorogenic acid content of 13 commercial instant coffees bought in the UK. Total chlorogenic acids ranged from 3.61 to 10.73%; the levels were 2.55-7.64% for total caffeoylquinic acids, 0.16-0.58% for total dicaffeoylquinic acids and 0.74-1.93% for total feruloyl quinic acids. The levels found depended on the extraction conditions and on differences between varieties. Data from other workers (summarized by Clifford, 1985) showed a similar range for total chlorogenic acids; Maier (1987a) found [2.7-8.9%] in five samples. The lower

figures resulted from use of darkly roasted coffees. The Working Group estimated that these values correspond to 54-215 mg/cup.

Glycosides: Viani (1988) estimated the content of atractyligenin at 0.8-0.9 mg/cup of arabica instant coffee and negligible for robusta.

Lipids: Instant coffees are generally free of lipids (and therefore the diterpenes, kahweol and cafestol), but many commercial brands are plated with about 0.3-0.5% coffee oil obtained by expression from roasted coffee or other methods to provide headspace aroma. Viani (1988) reported 0.02% oil and 0.0002% diterpenes in nonaromatized powder and 0.3% and 0.02%, respectively, in aromatized powder, corresponding to 0.4 mg/cup oil and 0.004 mg/cup diterpenes in nonaromatized powder and 7 mg/cup oil and 0.4 mg/cup diterpenes in aromatized powder. Certain commercial brands of instant coffee contain up to 10% by weight of very finely ground roasted coffee; this will increase these figures by 1.6% oil and 0.12% diterpenes in the powder, or 32 and 2.4 mg/cup, respectively, making this brew comparable with an espresso-type brew.

Trigonelline and nicotinic acid: Trigonelline has been determined in 12 UK commercial dry instant coffees by HPLC; an average of 1.37% (range, 0.94-1.69%) was found (Trugo *et al.*, 1983), [corresponding to 20-35 mg/cup, although the data on roasted coffee would suggest figures of 8-44 mg/cup]. Viani (1988) reported trigonelline at 5-15 mg/cup in 22 samples, which were therefore probably darkly roasted. In the same samples, nicotinic acid was found at 0.2-1.2 mg/cup; the data for roasted coffee suggest similar levels [0.4-1.6 mg/cup].

Acids: Of the nonvolatile acids, quinic, citric, malic and pyruvic acids are known to be present in fairly large quantities. Blanc (1977) reported on the total quantity of citric, malic, lactic and pyruvic acids and of the volatile acetic acid in instant coffees from four different countries. A range of 1.5-4.9% was found, which suggests that the acid content is increased only slightly as a consequence of industrial processing from roasted to dried extracts. Any increase occurring during extraction is balanced by loss during drying. Schormüller *et al.* (1961) reported average values of 2.20% citric acid, 0.50% malic acid, 0.45% lactic acid, 0.95% acetic acid and 0.08% pyruvic acid in dry instant coffee, to give a total of 4.18%, suggesting a marked increase in the level of acetic acid. Instant coffees derived from medium-roasted arabica coffee tend to have higher acid contents than darkly roasted robusta. Average levels of 3.8% (German instant coffees) and 2.3% (French instant coffee) result in [76 and 46 mg/cup], respectively.

Trace elements: The main mineral element in roasted and instant coffee is potassium, and levels can range from 3.6 to 5.9% in dry instant coffee (Clarke, 1985). Maier (1981) compiled data on all other elements present or likely to be present. In instant coffee, trace elements can originate both from the roasted coffee and from the water used for extraction: the content in the water can be at least tripled during

evaporation and drying of the extracts to the final product. Instant coffee is manufactured almost entirely in stainless-steel equipment, from which contamination is minimal (Clarke, 1985).

Other components: As a consequence of industrial extraction, higher percentages of melanoidins (see p. 71), polysaccharides and 'proteins' are found in instant coffee than in the soluble part of brewed coffee. Dissolution of a greater amount of polysaccharides is accompanied by some cleavage into constituent monoses, indicated by the presence of small quantitites of arabinose, galactose and mannose (Trugo, 1985).

(ii) *Volatile compounds*

Little quantitative information and few comprehensive listings are available of the volatile compounds present in commercial instant coffee. Certain volatile compounds, particularly sulfides and other non-polar substances, that occur preferentially in the oil of roasted coffee rather than in the carbohydrate matrix will be present as a result of 'aromatization' with coffee oil. Over 80 volatile compounds were identified in a commercial freeze-dried brew, including thiazoles, thiophenes, pyridines, pyrroles, pyrazines and furfurals (Dart & Nursten, 1985); the preparation was relatively rich in the latter two groups of compounds. In general, the volatile compounds found in brewed coffee can be expected to occur, to a greater or lesser extent.

Carbonyls: Methylglyoxal has been quantified in instant coffee by derivative GC (see also the monograph on methylglyoxal, p. 445), at levels of 23 ppm (μg/g; Hayashi & Shibamoto, 1985), 404-994 ppm (Shane *et al.*, 1988) and 70-217 ppm (Aeschbacher *et al.*, 1989). Kasai *et al.* (1982) found 100-150 μg/cup assuming 1.5 g of instant coffee for 100 ml water. Aeschbacher *et al.* (1989) also reported the presence of 13-42 μg/g diacetyl and 5-25 μg/g glyoxal in dry product.

Acids: The volatile and nonvolatile acid content of instant coffee is discussed above (pp. 80 and 86).

Esters: Methyl salicylate was found at 0-8.4 mg/l in nine samples of instant coffee (2 g powder/100 ml water; Swain *et al.*, 1985).

Furan- and sulfur-based compounds: Some compounds containing sulfur were quantified in instant coffee: furfuryl thiol, 3.90 ppm (mg/kg); 5-methyl furfuryl methyl disulfide, 0.015 mg/kg; and kahweofuran, 0.60 mg/kg. Three other furans have also been quantified (Tressl & Silwar, 1981). In general, these figures are comparable with those for roasted coffee, but when they are calculated as milligrams per cup they are quite low [e.g., kahweofuran, 1.2 μg/cup].

Pyrones: Tressl (1980) found more maltol (60-120 ppm (mg/kg)) than was expected.

Other compounds: Hydrogen peroxide has been detected at 180 ppm (mg/kg) in instant coffee (Aeschbacher *et al.*, 1989), and formaldehyde was found at 10-16.3 ppm (Hayashi *et al.*, 1986). Cyclotene, found at 70-110 mg/kg, occurred at a higher level than would have been expected from roasted coffees (Tressl, 1980).

No data were available to the Working Group on alcohols, nitrogen compounds, other sulfur compounds or phenols.

(*d*) *Compounds in decaffeinated coffee*

Under the Directives of the Commission of the European Communities (1977, 1985), dry decaffeinated instant coffees must contain no more than 0.3% caffeine; in practice, they contain less. This figure corresponds to 0-6 mg/cup of instant coffee brew, which also corresponds to that found (Barone & Roberts, 1984).

The solvents used in decaffeination may remove small quantities of aroma precursors, e.g., trigonelline, or increase their levels, e.g., amino acids and reducing sugars.

(*e*) *Additives and contaminants*

(i) *Flavouring additives*

Both roasted and instant coffees are largely marketed throughout the world as 100% pure coffee products, and are clearly labelled as such in developed countries (Commission of the European Communities, 1985). Blends are also available with many different kinds of roasted plant products, including chicory and malted and unmalted barley. Worldwide consumption in 1985 of dried chicory roots was estimated at 128 000 tonnes per annum, of which 32% was consumed in France, 55% in other European countries and 12% in South Africa. After roasting, chicory is mixed with both roasted and instant coffee, but no information was available on the quantities used. The quantities consumed annually of mixtures with barley vary considerably, in relation to the cost of coffee (Maier, 1987b).

(ii) *Other additives*

Preservatives are not used. Occasionally, roasted and instant coffees have been used as vehicles for vitamins and minerals. Flow agents (sodium aluminium silicates) may be incorporated in instant coffees used in vending machines (by national derogation in the Directive of the Commission of the European Communities).

(iii) *Contaminants*

For the purpose of this section of the monograph, the term 'contaminants' is used to mean those constituents sometimes present in the products, and therefore

in the beverages derived from them, which are not essential to the flavour and properties of the beverage. Some of these potential contaminants have known toxicological and, in some cases, carcinogenic effects.

Mycotoxins: Numerous studies, especially since 1965, have been conducted on the occurrence of mycotoxins in green coffee, and therefore in roasted and brewed coffee, due to the presence of mouldy beans. These studies were reviewed comprehensively by Strobel (1988b) and more briefly by Viani (1988). In particular, aflatoxin B_1 (see IARC, 1976a, 1987), ochratoxin A (see IARC, 1983, 1987) and, less often, sterigmatocystin (see IARC, 1976b) have been found in consignments of green coffees containing mouldy beans, although regulations seek to prevent such importation. Levels of aflatoxin B_1 at 3-12 ppb (μg/kg) in 2% of samples analysed, of ochratoxin A at 0.5-360 ppb in 3.5% of samples, and of sterigmatocystin at 1140 and 12 000 ppb in two very mouldy samples have been measured in some 2000 consignments examined. Decaffeinated green coffee beans that have been allowed to go mouldy show a greater tendency to develop toxins than nondecaffeinated coffee on account of the absence of the inhibitory action of caffeine. Ochratoxin A was found to be largely destroyed (80-99%) on roasting, as was aflatoxin B_1, to a slightly lesser extent.

Pesticides: Coffee beans are protected from pests within the cherry by direct application of pesticides, details of which have been reported (Mitchell, 1988; Snoeck, 1988). Coffee itself is consumed in the producing countries only after further processing, including roasting and brewing or extracting, which eliminate these contaminants almost quantitatively. Viani (1988) compiled available data on α- and β-hexachlorocyclohexanes, lindane, the DDT group, aldrin, dieldrin and others. Of six instant coffee samples, one contained 1.2 ng/g total hexachlorocyclohexanes and one contained 3 ng/g lindane, but no other pesticide was found. In contrast, 15 of 150 samples of green coffee had traces up to 290 ng/g lindane.

Nitrosamines: *N*-Nitrosopyrrolidine (see IARC, 1978) was found in five of ten instant coffees at 0.3-1.4 ppb (μg/kg) by Sen and Seaman (1981). The presence of this nitrosamine has been confirmed in two of seven samples of instant coffee by mass spectrometry as well as by liquid chromatography-thermal energy analysis at levels of 1.5 and 2.8 ppb (μg/kg). In one of six samples of roasted, ground coffee, *N*-nitrosopyrrolidine was found at a level of 0.4 ppb (μg/kg) (Sen *et al.*, 1990).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) *Perinatal exposure/oral administration*

Mouse: In a study available only as a preliminary report, groups of 150 male and 150 female Swiss mice (CRL:COBS, CD-1) were mated at 12 weeks of age, and mothers of mice to be allocated to treated groups received 1% instant coffee in the diet throughout gestation and lactation. After weaning, offspring were housed singly and received diets containing 0, 1, 2.5 or 5% (w/w) instant coffee [origin unspecified] until the end of the experiment at 720 days. Increasing levels of coffee in the diet impaired the growth of animals, but better survival was noted in animals that received the higher doses: at 24 months, the survival rate in the group receiving 5% instant coffee was 50% compared with about 25% in controls. Tumours of the liver, lung and lymphatic tissue were observed frequently. The incidences of benign liver-cell tumours in males were 42/150 controls, 38/150 receiving 1%, 20/150 receiving 2.5% and 16/150 receiving 5%; those in females were 2/150 controls, 2/150 receiving 1%, 1/150 receiving 2.5% and 1/150 receiving 5%. Two hepatocellular carcinomas were observed in one male mouse treated with 1% instant coffee and in one male mouse treated with 2.5%, but none was seen in mice receiving 5% or in controls. [The Working Group noted that hepatocellular tumours are common in Swiss mice.] No increase in the incidence of benign or malignant lung tumours was observed. Lymphosarcomas (all histological types) were observed in male and female control and treated animals. In males, the incidence of these tumours decreased from 32% in controls to 12% in the high-dose group. In females, no clear dose-dependent decrease was observed, although the incidence of lymphosarcomas was 46% in controls and 18% in the high-dose group (Stalder *et al.*, 1984). [The Working Group noted that the reduced numbers of liver adenomas in males and of lymphosarcomas in animals of each sex in the higher-dose groups might have been due to impaired growth; these animals also had longer survival. Neither of these factors was taken into account in the analysis.]

Rat: Groups of 55 male and 55 female F_1 Sprague-Dawley rats, five to six weeks old, were given 25, 50 or 100% freshly brewed coffee as drinking fluid *ad libitum* for two years, at which time all survivors were killed. The animals were derived from females given 50% coffee as drinking fluid for about five weeks before mating and throughout gestation and lactation. Parent males, parent control

females and two groups of F_1 control rats received tap-water only. Ten rats of each sex per group were killed at one year and were submitted to blood sampling and necropsy. Lower mean body weights were observed in males that received 100% coffee, and significantly increased mortality was seen in females given 50 and 100% coffee. Two statistical methods were used to adjust the incidence data for survival differences: In the first, which assumes that tumours are non-fatal (i.e., incidental), a significant increase in the number of tumour-bearing males was seen in the low-dose group (relative risk (RR), 1.26; $p < 0.05$) but in no other group. In the second analysis, which assumes that tumours are lethal, increased numbers of tumour-bearing animals were seen among males in the low- and mid-dose groups (RR, 1.71, $p < 0.01$ and 1.43, $p < 0.05$, respectively) and among females in the mid- and high-dose groups (RR, 1.47, $p < 0.05$ and 1.45, $p < 0.05$, respectively) (Palm *et al.*, 1984). [The Working Group noted that the first statistical analysis was more appropriate, since the tumours were not the cause of death.]

(*b*) *Oral administration*

Rat: In a study reported as a letter to the Editor of *The Lancet*, 144 male and 144 female Sprague-Dawley rats, 21 days of age, were administered 5% instant coffee in the diet for two years, at which time the survivors were killed. An untreated control group of 41 males and 41 females was available. The urinary bladders of 94 male and 99 female treated and 29 male and 29 female control animals were examined histologically. No hyperplasia or tumour of the urinary bladder was observed (Zeitlin, 1972). [The Working Group noted the incomplete reporting of the study: no information on survival was given, and only the bladder was examined histologically.]

Groups of 40 male and 40 female Sprague-Dawley rats, weighing approximately 100 g, were fed diets containing 6% of 13 different samples of instant coffee; caffeine had been removed by extraction with dichloromethane from seven of the samples, but in three of these the caffeine had been put back. Treatment was for two years, at which time all survivors were killed. A control group of 40 males and 40 females was available. Survival was similar in all groups, although males given the decaffeinated coffees had slightly lower death rates, but the body weights of treated males were lower than those of controls. No increase in the incidence of any type of tumour was noted. In males in two of the six groups given instant coffee and in one of the three groups given decaffeinated coffee plus caffeine (see also the monograph on caffeine p. 310), the incidence of benign and malignant tumours was significantly lowered (all $p < 0.05$); in females, the decrease was not statistically significant. A logistic regression analysis showed that the level of caffeine significantly lowered the incidence of tumours (Würzner *et al.*, 1977a,b). [The Working Group noted that only one control group was used for the 13 treatment

groups and that the reduced numbers of tumours might have been due to impaired growth.]

(*c*) *Administration with known carcinogens*

The Working Group was aware of various other experiments (e.g., Mori & Hirono, 1977; Fujii *et al.*, 1980; Wattenberg & Lam, 1984; Nishikawa *et al.*, 1986) that were part of studies on the modifying effects of coffee on the activity of known carcinogens, which are not included here since their design was inadequate to reveal any effect of coffee on tumour production (short duration of exposure and/or limited numbers of animals).

(i) *Azaserine*

Rat: Groups of 40 male SPF Wistar rats, 19 days of age, were given a single intraperitoneal injection of azaserine, a pancreatic carcinogen, at 30 mg/kg bw and were then fed a low-fat diet, a high-fat diet or a high-fat diet plus coffee solution as the drinking fluid. The concentration of coffee was increased gradually from 25% during the first two weeks to 100% within four weeks, which was continued for the life span of the animals. Animals were autopsied 15 months after the end of azaserine treatment. The mean body weight of rats given the high-fat diet and coffee was significantly lower than that of the high-fat controls. The number of pancreatic tumours was significantly smaller in the group maintained on the high-fat diet and coffee than in the group on a high-fat diet only (44 adenomas *versus* 176 [$p < 0.001$] and 28 carcinomas *versus* 57 [$p < 0.05$]) (Woutersen *et al.*, 1989). [The Working Group noted that the decrease could have been due, at least partly, to the impaired growth of the animals.]

(ii) *7,12-Dimethylbenz[a]anthracene*

Rat: Groups of 40-41 female Sprague-Dawley rats, 53-55 days of age, were given a single intravenous injection of 7,12-dimethylbenz[*a*]anthracene (DMBA) at 20 mg/kg bw. Coffee (moderate or full strength) and decaffeinated (97% caffeine-free) coffee were given instead of drinking-water 29 days before up to three days after DMBA treatment; the experiment was terminated 12-18 weeks after DMBA treatment. Further groups of 80 or 84 female rats received a single dose of DMBA at 5 mg by gavage at 54 or 55 days of age and three days later were given coffee in the drinking fluid until 18-21 weeks after DMBA treatment. After DMBA treatment, all rats were palpated at two-week intervals for the presence of mammary tumours. When tumours reached 2 cm in diameter, they were excised surgically, and the rat was placed back in the experiment. In rats treated by intravenous administration of DMBA, moderate and high doses of coffee significantly ($p < 0.05$) reduced the number of mammary carcinomas per rat. Consumption of high

and moderate doses of decaffeinated coffee did not have this effect, but addition of caffeine at 860 mg to decaffeinated coffee resulted in a significant reduction ($p < 0.05$) in the number of mammary carcinomas per animal. Coffee consumption did not significantly affect the percentage of rats with mammary tumours. Administration of coffee to rats treated with DMBA by gavage did not significantly affect the number of mammary carcinomas per animal (Welsch *et al.*, 1988).

In a subsequent study with the same experimental protocol (intravenous and gastric administration of DMBA) but with administration of a chemically defined diet containing 5% unsaturated fat (corn oil) *ad libitum*, similar results with coffee were obtained, i.e., a reduction in the number of mammary tumours per rat but no effect on the percentage of rats with tumours (Welsch & DeHoog, 1988).

Hamster: Groups of 20 female Syrian golden hamsters, weighing approximately 70 g, were fed powdered chow or chow supplemented with 20% powdered green coffee beans. Two weeks later, the right buccal pouch of 16 animals from each group was painted three times with a 0.5% solution of DMBA in heavy mineral oil; the remaining four animals per group were treated three times weekly with heavy mineral oil alone and served as controls. The experiment was terminated after a total of 50 treatments (16.5 weeks). At the end of the experiment, 12/16 animals given chow alone and 9/16 also given green coffee beans were still alive; most of the losses were due to respiratory infections or ether anaesthesia. Tumours of the buccal pouch were seen in 9/12 animals receiving chow (eight had multiple tumours) and 2/9 also receiving green coffee beans. Two hamsters receiving chow had mild to moderate dysplasia of the right buccal pouch and one had dysplasia, including carcinoma *in situ*; the buccal pouches of the nine remaining animals had various grades of dysplasia, including carcinoma *in situ* and papillary carcinomas. Of the animals receiving green coffee beans, only two had carcinomas of the right buccal pouch; the remaining seven showed dysplasia. A statistically significant reduction in average tumour mass was observed in the latter group (Miller *et al.*, 1988). [The Working Group noted that survival was low.]

(iii) N-*Nitrosobis(2-oxypropyl)amine*

Hamster: Groups of 40 male Syrian golden hamsters, six weeks old, received two weekly subcutaneous injections of 20 mg/kg bw *N*-nitrosobis(2-oxypropyl)-amine and were then fed a low-fat diet, a high-fat diet or a high-fat diet plus daily preparations of coffee as the drinking fluid. The concentration of coffee was gradually increased from 25% during the first two weeks to 100% within four weeks, which was continued for the life span of the animals. The hamsters were killed 12 months after the second injection of nitrosamine, and autopsied. Mean body weights of animals on high-fat diet alone were significantly greater than those of animals on low-fat diet; those of hamsters fed high-fat diets with caffeine did not

differ significantly from those of animals on the high-fat diet alone. The total number of ductal/ductular adenocarcinomas of the pancreas was significantly increased in the high-fat group (eight; $p < 0.05$) as compared to the low-fat group (two). The total number of adenocarcinomas in the group receiving high-fat diet plus coffee (five) was slightly but not significantly smaller than that in the group on high-fat diet alone (Woutersen *et al.*, 1989).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, metabolism and excretion*

No data were available to the Working Group (see the monograph on caffeine p. 321).

(ii) *Toxic effects*

Groups of male Wistar rats were given 4 or 8% brewed or decaffeinated coffee in the drinking-water for six to eight months. Body weights of coffee-treated rats were 6-7% lower than those of controls receiving water only. Coffee induced 'no untoward effect' on the liver (Strubelt *et al.*, 1973).

Weanling male Sprague-Dawley rats were fed starch-based diets supplemented with either brewed coffee, decaffeinated coffee, tea, caffeine or nothing (controls). Compared with controls, rats consuming coffee or caffeine had elevated concentrations of cholesterol and phospholipids. In addition, both groups had lower levels of triglycerides, although the difference was significant only for the group receiving caffeine (Naismith *et al.*, 1969).

Six male and nine female adult rhesus monkeys were fed an atherogenic diet *ad libitum* for 12 months. Major changes in the profiles of total plasma lipids and lipoproteins occurred within three to six months and remained at the higher level thereafter. Four females and three males were then given 50% coffee as drinking fluid for 12 months, while the remaining animals were given water. The authors reported no significant difference in total plasma protein or lipids between coffee-treated and control animals after 15 and 18 months (Callahan *et al.*, 1979).

In a study reported as an abstract, coffee did not enhance the number or size of pancreatic atypical acinar-cell foci induced in rats by azaserine (Roebuck *et al.*, 1985).

(iii) *Effects on reproduction and prenatal toxicity*

Brewed coffee: In a combined subchronic, reproductive and developmental toxicity study, Sprague-Dawley rats were given 12.5, 25 or 50% freshly percolated

coffee as the drinking fluid (daily caffeine intake, 9, 19 or 38 mg/kg bw) for five weeks before mating, throughout gestation and until 27 days after parturition. No effect on fertility, litter size, neonatal growth or survival was observed with any dose level. Among the offspring, underdevelopment of the renal pelvis was observed in the mid- and high-dose groups; cleft palate and delayed ossification were also observed in the offspring, but these were not clearly dose-related (Palm *et al.*, 1978).

In a similarly designed study, Sprague-Dawley rats received 25, 50 or 100% percolated coffee as the drinking fluid (approximate daily caffeine intake, 20, 40 or 80 mg/kg bw) for 91 days, after which they were mated to produce F_{1a} litters, while the administration of coffee continued. Female rats were mated again ten days after their first litters had been weaned to produce F_{1b} litters, which were used for teratological examination. Parent rats treated with 50 and 100% coffee had enlarged livers and kidneys, but no significant effect on reproduction or lactation was observed. Body weights of F_{1a} offspring of the high-dose rats were comparable to those of controls at four days of age but had decreased significantly by weaning at 21 days of age. No teratogenic effect or decrease in neonatal body weight was observed in F_{1b} pups delivered by caesarean section, although offspring of rats given the mid- and high doses showed a significantly increased incidence of delayed ossification of the sternebrae (Nolen, 1981).

In a behavioural teratology study, Sprague-Dawley rats were given either drinking-water or fresh drip coffee as drinking fluid from the time of mating until parturition. The average daily dose of caffeine was 122 mg/kg bw. Significant decreases in body, liver and brain weights were observed in the offspring of the coffee-treated group at birth but not at 30 days of age. In addition, a significant increase in motor activity and a decrease in grooming time and time spent with a novel object were observed in this group at 30 days of age (Groisser *et al.*, 1982).

In another behavioural study, Sprague-Dawley rats received 0, 25 or 100% brewed coffee as the drinking fluid from 60 days before mating until weaning of the F_1 offspring. No effect on reproduction was observed. Among the offspring of treated rats, there were delays in the eruption of incisor teeth and maturation of swimming skills. A significant decrease in running wheel and preweaning open-field activities was also observed, but no effect was seen on learning, memory or motor function. On the basis of post-weaning measurements, the authors concluded that the treatment did not result in a significant risk for irreversible damage in the offspring (Butcher *et al.*, 1984).

Instant coffee: In a combined subchronic, reproductive and developmental toxicity study of instant coffee (Nolen, 1981), described above, the body weights of F_{1a} offspring of high-dose dams were comparable to those of controls at four days of age but had decreased significantly by weaning at 21 days of age. No teratogenic effect or decrease in fetal body weight was observed in F_{1b} pups delivered by

caesarean section, although offspring of the high-dose group had a significantly increased incidence of delayed ossification of the sternebrae.

Groups of white mice [strain unspecified] were fed instant coffee crystals in the diet, at doses equivalent to human consumption of 0, 4, 8, 12, 16 or 20 cups of coffee per day, from the time of mating to parturition. No abnormality or gross malformation of the alimentary tract was observed in the offspring, but pup body weight and length were significantly decreased at doses equivalent to eight cups of coffee or more (Murphy & Benjamin, 1981).

Sprague-Dawley rats were given 1.5% (w/v) solvent-free, freeze-dried coffee solution as the drinking fluid from the time of mating until gestation day 21 or postnatal day 14. When treatment was continued until postnatal day 14, offspring of coffee-treated and control groups were cross-fostered. No gross malformation, difference in organ or fetal body weights, or change in iron, zinc or copper levels in maternal plasma, liver or kidney or in fetal liver were observed. Offspring of dams treated with coffee prenatally had significantly decreased birth weights; no change in body weight was observed three or four days after birth (Muñoz *et al.*, 1986).

Decaffeinated coffee: In a combined subchronic, reproductive and developmental toxicity study, Sprague-Dawley rats received 25, 50 or 100% decaffeinated brewed and instant coffee as the drinking fluid (equivalent to 12, 25 or 50 cups of coffee per day) with the same study design as described previously (Nolen, 1981). No effect on reproduction, litter size or postnatal viability of the F_{1a} litters was observed. Body weights of offspring of mid- and high-dose dams were comparable to those of controls at four days of age but were significantly decreased at weaning. No malformation or variation was observed in F_{1b} offspring, and no delay in ossification was seen (Nolen, 1982).

In a behavioural teratology study, Sprague-Dawley rats received freshly brewed decaffeinated coffee (average daily caffeine intake, 4.5 mg/kg bw) as the drinking fluid from the time of mating until parturition. A significant decrease in the liver weights of the offspring was observed at birth, and a significant increase in motor activity and a decrease in time spent grooming or with a novel object were seen (Groisser *et al.*, 1982).

(iv) *Genetic and related effects*

The genetic and related effects of various types of coffee have been reviewed (Sugimura, 1982; Sugimura & Sato, 1983; Aeschbacher *et al.*, 1984a; Nagao *et al.*, 1984; Sugimura *et al.*, 1984; Nagao *et al.*, 1986b; Aeschbacher, 1990). In bacteria, there is evidence that dicarbonyls (e.g., methylglyoxal) and hydrogen peroxide acting together contribute to the mutagenic activity of roasted coffee (Nagao *et al.*, 1984; Fujita *et al.*, 1985a,b). Both the dicarbonyls and hydrogen peroxide may be deactivated by enzymes present in cells and tissue, such as glyoxalase, glutathione

(for methylglyoxal), catalase and peroxidase (for hydrogen peroxide) (Nagao *et al.*, 1984; Friederich *et al.*, 1985; Fujita *et al.*, 1985b; Tucker *et al.*, 1989). In mammalian cells, coffee aroma stripped from roasted coffee and the dicarbonyls contained therein may contribute to the genetic effects (Aeschbacher *et al.*, 1985; Tucker *et al.*, 1989). There is substantial evidence in various genetic test systems, with one exception (Graf & Würgler, 1986), that caffeine is not involved in the genetic activity observed (Nagao *et al.*, 1979; Aeschbacher, 1990).

Coffee has been studied in experimental genetic and related systems as both instant coffee powders and as finely ground roasted coffee beans prepared with water in the normal way for drinking and then lyophilized. The doses are expressed as mass of coffee powder used in the treatment, which generally required the powder to be dissolved in the treatment solvent. Sterilization of preparations to be tested for bacterial mutagenicity, by filtration or autoclaving, did not influence the results significantly (Aeschbacher *et al.*, 1980). Time between sample preparation and test may affect the genetic response. In several studies, where specifically noted, the coffee was solvent-extracted or chemically fractionated. Studies in bacteria of green coffee beans indicate a lack of mutagenic activity (Kosugi *et al.*, 1983; Albertini *et al.*, 1985; Dorado *et al.*, 1987); similar comparisons of roasted and unroasted beans have not been made with other systems.

The results of the studies on genetic and related effects are listed at the end of this section in Table 29, with the evaluation of the Working Group, as positive, negative or inconclusive, as defined in the footnotes. The results are tabulated separately for the presence and absence of an exogenous metabolic activation system. The lowest effective dose (LED), in the case of positive results, and the highest ineffective dose (HID), in the case of negative results, are shown together with the appropriate reference. The studies are summarized briefly below.

Brewed coffee: Freshly brewed coffee induced prophage lambda in lysogenic *Escherichia coli* K12.

A number of studies have been conducted on the mutagenicity of coffees to *Salmonella typhimurium* under different conditions. Brewed coffee consistently induced mutations in *S. typhimurium* TA100, and mutations were also induced in TA102 and TA104, which are more sensitive to oxidative mutagens, and in *E. coli* WP2 *uvrA*/pKM101. There are conflicting reports on the mutagenicity of coffee to *S. typhimurium* TA98. [The Working Group noted the inadequate reporting of several of the studies with TA98.] Coffee gave negative results in standard strains of *S. typhimurium*, which do not contain the pKM101 plasmid. Brewed coffee was also mutagenic in the *S. typhimurium* L-arabinose-resistance forward mutation assay in strain BA13.

There was no significant response in tests for sex-linked recessive lethal mutation, dominant lethal mutation or chromosome loss in *Drosophila*

melanogaster, but weak activity was observed in the somatic cell (wing imaginal disc) mutation and mitotic recombination tests following larval feeding. These effects were attributed to caffeine.

Treatment of cultured human lymphocytes with brewed coffee induced sister chromatid exchange, gaps, breaks and total chromosomal aberrations. Endoreduplicated cells were induced in Chinese hamster ovary AUXB1 cells. Bisulfite, which complexes carbonyls, reduced the frequency of sister chromatid exchange and endoreduplicated cells, while catalase and peroxidase treatment had no effect (Tucker *et al.*, 1989). Coffee aroma stripped from roasted coffee beans also induced gaps, breaks and total chromosomal aberrations in human peripheral lymphocytes.

Instant coffee: Instant coffee induced prophage lambda in lysogenic *E. coli* K12, strain GY5027 but did not induce SOS activity in *S. typhimurium* TA1535/pSK1002.

Instant coffee induced mutations in *S. typhimurium* TA100 but not in TA98, TA1535, TA1537 or TA1538. Instant coffees were mutagenic to *S. typhimurium* strains TA102 and TA104, which are more sensitive to oxidative mutagens. Instant coffee was also active in the *S. typhimurium* L-arabinose-resistance forward mutation assay in strain BA13. The mutagens in coffee are inactivated by the cytosolic fraction of exogenous metabolic systems from rat liver, by heat in the presence of oxygen (Friederich *et al.*, 1985), by sodium sulfite (Suwa *et al.*, 1982) and by catalase (Fujita *et al.*, 1985b). This evidence, together with that from other studies, led to the conclusion that an interaction of methylglyoxal with hydrogen peroxide accounts for most of the mutagenicity of instant coffee (Fujita *et al.*, 1985a,b).

Negative results were obtained in host-mediated assays in which coffee was administered to male Swiss mice by gavage after intraperitoneal injection of *S. typhimurium* TA1530. Similarly, negative results were obtained in the intrasanguinous test following intravenous injection of *E. coli* K12 into male Swiss mice and assaying for reverse and forward mutation at the *nia*$^+$ and *gal*$^+$ loci, respectively.

Treatment of Chinese hamster lung cells with instant coffee increased the frequency of mutations in the diphtheria toxin resistance assay. Most of the mutagenicity was suppressed by sodium bisulfite. Methylglyoxal was shown to account for less than 3% of the mutagenicity (Nakasato *et al.*, 1984).

There was no significant response in tests for sex-linked recessive lethal mutation, dominant lethal mutation or chromosome loss in *Drosophila melanogaster*, but weak activity was observed in the somatic cell (wing imaginal

disc) mutation and mitotic recombination tests following larval feeding. These effects were attributed to caffeine.

Treatment of cultured human lymphocytes with instant coffee induced gaps, breaks and total chromosomal aberrations. Sister chromatid exchange and endoreduplicated cells were induced in Chinese hamster ovary AUXB1 cells (Tucker *et al.*, 1989).

Instant coffee administered to Chinese hamsters as a single oral dose did not increase the frequency of sister chromatid exchange. In a micronucleus test, Swiss mice were given five consecutive daily oral doses of instant coffee; no significant induction of micronuclei above spontaneous levels was observed. Two oral doses to Swiss mice of coffee aroma (up to 50 ml/kg bw) also gave negative results (Aeschbacher *et al.*, 1984b). In another study, no significant increase in the frequency of micronuclei was induced by single or multiple administrations of instant coffee by gavage (Shimizu & Yano, 1987). [The Working Group noted that the authors reported a tendency for the number of micronuclei to increase in a dose-related fashion.]

Decaffeinated coffee: Decaffeinated coffee induced prophage lambda in lysogenic *E. coli* K12, strain GY5027. It induced mutation in *S. typhimurium* TA98, TA100, TA102 and TA104, which are sensitive to oxidative mutagens. No effect was observed in *Drosophila melanogaster* when decaffeinated coffee was assayed for the induction of somatic cell (wing imaginal disc) mutation and mitotic recombination. Treatment of cultured human lymphocytes with decaffeinated coffee induced gaps, breaks and total chromosomal aberrations. Sister chromatid exchange and endoreduplicated cells were induced in Chinese hamster ovary AUXB1 cells (Tucker *et al.*, 1989).

Coffee in combination with known mutagens: Brewed coffee, instant coffee and decaffeinated coffee suppressed SOS induction by ultra-violet light, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, 4-nitroquinoline-*N*-oxide and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in *S. typhimurium* TA1535/pSK1002 (Obana *et al.*, 1986). Instant, decaffeinated and brewed coffee inhibited mutagenesis resulting from the nitrosation of methylurea in *S. typhimurium* TA1535 (Stich *et al.*, 1982).

In mouse bone-marrow micronucleus tests, positive responses to mitomycin C, cyclophosphamide and procarbazine (but not adriamycin) were significantly reduced by administration of instant coffee 2 h before the clastogens. Similar effects were observed with decaffeinated and brewed coffee on the micronucleating effect of mitomycin C, and with brewed coffee on the effect of procarbazine (Abraham, 1989). In contrast, it has been reported that instant coffee caused no significant alteration in the incidence of micronuclei induced by *N*-nitroso-dimethylamine (Shimizu & Yano, 1987).

Table 29. Genetic and related effects of brewed, instant and decaffeinated coffee

Test system	Results		Dose[a] LED/HID	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Brewed coffee				
PRB, λ Prophage induction in E. coli K12, strain GY5027	+	0	5700.0000	Kosugi et al. (1983)
PRB, λ Prophage induction in E. coli, strain GY5022	–	0	21400.0000	Kosugi et al. (1983)
SAF, Salmonella typhimurium BA13, forward mutation to AraR	+	0	1000.0000	Dorado et al., (1987)
SAF, Salmonella typhimurium BA13, forward mutation to AraR	+	0	500.0000	Ariza et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	7000.0000	Nagao et al. (1979)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	12500.0000	Aeschbacher & Wurznèr (1980)
SA0, Salmonella typhimurium TA100, reverse mutation	+	(+)	5000.0000	Shane et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	0	6000.0000	Kosugi et al. (1983)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	50000.0000	Kam (1980)
SA2, Salmonella typhimurium TA102, reverse mutation	+	(+)	2500.0000	Shane et al. (1988)
SA4, Salmonella typhimurium TA104, reverse mutation	+	(+)	5000.0000	Shane et al. (1988)
SA5, Salmonella typhimurium TA1535, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA7, Salmonella typhimurium TA1537, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA8, Salmonella typhimurium TA1538, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	0.0000	Nagao et al. (1979)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA9, Salmonella typhimurium TA98, reverse mutation	+	–	50000.0000	Kam (1980)
ECR, E. coli WP2 uvrA/pKM101, reverse mutation	+	0	7500.0000	Kosugi et al. (1983)
DMN, Drosophila melanogaster, sex chromosome losses	–	0	30000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, somatic mutation (larval feeding)	(+)	0	30000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, mitotic recombination	(+)	0	30000.0000	Graf & Wurgler (1986)
DMX, Drosophila melanogaster, sex-linked recessive lethal mutation	–	0	30000.0000	Graf & Wurgler (1986)
DML, Drosophila melanogaster, dominant lethal test	–	0	30000.0000	Graf & Wurgler (1986)
SIC, Chinese hamster ovary AUXB1, sister chromatid exchange	+	0	200.0000	Tucker et al. (1989)
CHL, Chromosomal aberrations, human lymphocytes in vitro	+	+	2500.0000	Aeschbacher et al. (1985)
SHL, Human peripheral lymphocytes, sister chromatid exchange, in vitro	+	0	300.0000	Tucker et al. (1989)
MVH, Micronuclei, human (splenectomised) erythrocytes/reticulocytes in vivo	+	0	0.0000	Smith et al. (1990)

Table 29 (contd)

Test system	Results		Dose[a] LED/HID	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Instant coffee				
PRB, λ Prophage induction in E. coli K12, strain GY5027	+	0	5700.0000	Kosugi et al. (1983)
PRB, SOS repair	–	0	9000.0000	Obana et al. (1986)
PRB, λ Prophage induction in E. coli GY5022	–	0	21400.0000	Kosugi et al. (1983)
SAF, Salmonella typhimurium BA13, forward mutation	+	0	500.0000	Dorado et al., (1987)
SAF, Salmonella typhimurium BA13, forward mutation	+	0	500.0000	Ariza et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	1500.0000	Nagao et al. (1979)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	17500.0000	Aeschbacher & Wurzner (1980)
SA0, Salmonella typhimurium TA100, reverse mutation	+	(+)	12500.0000	Shane et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	0	5000.0000	Aeschbacher et al. (1989)
SA2, Salmonella typhimurium TA102, reverse mutation	+	0	10000.0000	Aeschbacher et al. (1989)
SA2, Salmonella typhimurium TA102, reverse mutation	+	+	5000.0000	Shane et al. (1988)
SA4, Salmonella typhimurium TA104, reverse mutation	+	+	10000.0000	Shane et al. (1988)
SA5, Salmonella typhimurium TA1535, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA7, Salmonella typhimurium TA1537, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA8, Salmonella typhimurium TA1538, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	0.0000	Nagao et al. (1979)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	25000.0000	Aeschbacher & Wurzner (1980)
DMN, Drosophila melanogaster, sex chromosome losses	–	0	40000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, somatic mutation	(+)	0	40000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, mitotic recombination	(+)	0	40000.0000	Graf & Wurgler (1986)
DMX, Drosophila melanogaster, sex-linked recessive lethal mutation	–	0	40000.0000	Graf & Wurgler (1986)
DML, Drosophila melanogaster, dominant lethal test	–	0	40000.0000	Graf & Wurgler (1986)
GCL, Chinese hamster lung (CHL) cells, diphtheria toxin resistance	+	0	4000.0000	Nakasato et al. (1984)
CHL, Chromosomal aberrations, human lymphocytes in vitro	+	+	25000.0000	Aeschbacher et al. (1985)
HMM, Host mediated assay, Salmonella typhimurium TA1530 in Swiss mice	–	0	6000.0000	Aeschbacher & Wurzner (1980)
HMM, Intrasanguinous test, E. coli , Swiss mice	–	0	6000.0000	Aeschbacher & Wurzner (1980)
SIC, Chinese hamster ovary AUXB1, sister chromatid exchange	+	0	200.0000	Tucker et al. (1989)
SVA, Sister chromatid exchange, Chinese hamsters in vivo	–	0	2500.0000	Aeschbacher et al. (1984b)
MVM, Micronucleus test, Swiss mice in vivo	–	0	3000.0000	Aeschbacher et al. (1984b)
MVM, Micronucleus test, ddy mice in vivo	–	0	2500.0000	Shimizu & Yano (1987)
MVM, Micronucleus test, ddy mice in vivo	–	0	1000.0000	Shimizu & Yano (1987)

Table 29 (contd)

Test system	Results		Dose[a] LED/HID	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
Decaffeinated coffee				
PRB, λ Prophage induction in E. coli K12, strain GY5027	+	0	5700.0000	Kosugi et al. (1983)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	1500.0000	Nagao et al. (1979)
SA0, Salmonella typhimurium TA100, reverse mutation	+	(+)	2500.0000	Shane et al. (1988)
SA0, Salmonella typhimurium TA100, reverse mutation	+	–	50000.0000	Kam (1980)
SA2, Salmonella typhimurium TA102, reverse mutation	+	(+)	5000.0000	Shane et al. (1988)
SA4, Salmonella typhimurium TA104, reverse mutation	+	(+)	5000.0000	Shane et al. (1988)
SA9, Salmonella typhimurium TA98, reverse mutation	–	–	0.0000	Nagao et al. (1979)
SA9, Salmonella typhimurium TA98, reverse mutation	+	–	50000.0000	Kam (1980)
DMM, Drosophila melanogaster, somatic mutation	–	0	200000.0000	Graf & Wurgler (1986)
DMM, Drosophila melanogaster, mitotic recombination	–	0	200000.0000	Graf & Wurgler (1986)
SIC, Chinese hamster ovary AUXB1 cells, sister chromatid exchange	+	0	300.0000	Tucker et al. (1989)
CHL, Chromosomal aberrations, human lymphocytes in vitro	+	+	2500.0000	Aeschbacher et al. (1985)

[a]Expressed as dry weight of extract

(*b*) *Humans*

(i) *Toxic effects*

Coffee drinking has been associated with a number of adverse effects (Goldman, 1984; Spiller, 1984c; Stone, 1987). Many of the undesirable effects of coffee have been ascribed to caffeine, and they are dealt with in the respective monograph; at least some of the effects of coffee on plasma cholesterol and lipids, however, can be attributed to ingredients other than caffeine.

A weak association was seen between coffee drinking and total mortality among men in a 25-year follow-up from the Netherlands. No cause-specific mortality was reported (Vandenbroucke *et al.*, 1986).

Plasma cholesterol and lipoproteins: A series of epidemiological studies have investigated possible associations between coffee drinking and serum cholesterol levels; these have been reviewed (Thelle *et al.*, 1987). Many of the studies found that coffee consumption was positively associated, to variable degrees, with levels of total serum cholesterol in people of each sex (Thelle *et al.*, 1983; Kark *et al.*, 1985; Klatsky *et al.*, 1985; Tuomilehto *et al.*, 1987; Aro *et al.*, 1989). Other investigators found some association in men or women (Nichols *et al.*, 1976; Shirlow & Mathers, 1984; Mathias *et al.*, 1985; Curb *et al.*, 1986; Pietinen *et al.*, 1988) or in only some segments of the general population, e.g., individuals with coronary heart disease (Little *et al.*, 1966) or hypertension (Davis *et al.*, 1988). There are also a number of studies in which no association was observed (Phillips *et al.*, 1981; Hofman *et al.*, 1983; Kovar *et al.*, 1983; Aro *et al.*, 1985; Donahue *et al.*, 1987; Paoletti *et al.*, 1989).

Only a few scientists have investigated the relationship between coffee consumption and the concentration of individual serum lipoproteins. A positive association was observed between the level of low-density lipoproteins and coffee intake, whereas no such relation was seen with high-density lipoproteins or triglycerides (Førde *et al.*, 1985; Aro *et al.*, 1987; Bak & Grobbee, 1989; Paoletti *et al.*, 1989).

The conflicting data on the effects of coffee on serum cholesterol may be due to the use of different methods in the preparation of coffee. Thus, boiled coffee, but not filtered coffee, raised serum cholesterol (0.5-1.0 mmol/l) in three separate clinical trials conducted in Norway, Finland and the Netherlands (Førde *et al.*, 1985; Aro *et al.*, 1987; Bak & Grobbee, 1989). Epidemiological observations agree with the results of these clinical trials (Stensvold *et al.*, 1989; Pietinen *et al.*, 1990). Zock *et al.* (1990) suggest that a nonsaponifiable lipid fraction, isolated from boiled coffee by ultracentrifugation, raised serum cholesterol in healthy volunteers.

Coronary heart disease: The results of the Boston Collaborative Drug Surveillance Program (1972) suggest that consumption of more than five cups of coffee per day doubles the risk for myocardial infarction, as compared to no consumption at all. Similar results were reported by other investigators (Jick *et al.*, 1973; Mann & Thorogood, 1975; LaCroix *et al.*, 1986; LeGrady *et al.*, 1987; Rosenberg *et al.*, 1988). Some established only a modest association between myocardial infarction and heavy coffee consumption and for only some segments of the population (Rosenberg *et al.*, 1980, 1987; La Vecchia *et al.*, 1989a). Several other epidemiological studies found no association (Klatsky *et al.*, 1973; Dawber *et al.*, 1974; Hennekens *et al.*, 1976).

In some studies, the apparent association between coffee drinking and ischaemic heart disease can be accounted for by cigarette smoking (Hennekens *et al.*, 1976; Wilhelmsen *et al.*, 1977; La Vecchia *et al.*, 1989a).

[The Working Group was not aware of any longitudinal study on the association between coffee intake and the risk of coronary heart disease from populations with high consumption of boiled coffee.]

(ii) *Effects on reproduction and prenatal toxicity*

The reproductive effects of coffee on humans have been reviewed (Ernster, 1984; Leviton, 1984; James & Paull, 1985; Pieters, 1985; Heller, 1987; Schneider, 1987; Leviton, 1988). Most epidemiological studies have been affected by a number of methodological issues, including (i) inadequate measurement of intake: almost all studies relied on reported intakes; some studies were limited to coffee consumption and ignored other sources of caffeine; and most studies ignored distinctions between different types of preparation and different strengths of coffee; (ii) inadequate control for the possible confounding effects of variables such as smoking, alcohol consumption, age, nutrition and life-style factors in some studies; (iii) low response rates in several studies; (iv) biased selection of adequate controls because of self-selection into groups of drinkers and nondrinkers of coffee; (v) recall bias in retrospective studies, particularly those of malformations; and (vi) insufficient statistical power in some of the studies. Despite these limitations, epidemiological studies are the single source of information on human reproductive effects of coffee.

Malformations: Borlée *et al.* (1978) identified 202 infants with congenital malformations of any type among 17 970 births in eight Belgian hospitals between 1972 and 1974. A group of 175 control infants was also selected. The parents of cases and controls were interviewed about consumption of coffee and other possible risk factors. Compared to women who did not drink coffee, the relative risks (RR) were calculated by the Working Group to be [0.7] for women drinking one to four cups per day, [0.8] for those drinking five to seven cups and [1.5] for

those drinking eight or more cups. In a chi-square test, the linear trend was barely significant [(p = 0.05)]. No significant association was found between coffee drinking and smoking or use of medicines. [The Working Group noted that no information was given on refusals or other losses, that the possibility of recall bias was not considered, and that there was no proper control of confounding variables.]

Jacobson *et al.* (1981) reported three cases of infants with ectrodactyly born to women who drank eight to 25 cups of percolated coffee per day. The women were selected from among those who contacted the authors after reading press accounts of the relationship between coffee drinking and malformations. [The Working Group noted that this letter to the Editor constitutes only anecdotal information.]

Linn *et al.* (1982) studied the association between coffee consumption and several outcomes of pregnancy in 12 205 women in Boston, MA, USA, in 1977-80, who represented 71% of women giving birth in one hospital. Women were interviewed one to two days after delivery about their previous medical and obstetric history and habits, including coffee and tea consumption during the first trimester. Diabetic and asthmatic women and those with multiple pregnancies were excluded. The analysis was controlled for a number of confounding factors. No association was found between coffee drinking and the frequency of malformations.

The association between drinking caffeine-containing beverages and six types of malformation (inguinal hernia, oral clefts, cardiac defects, pyloric stenosis and neural tube defects) was studied in a case-control study of 2030 children from a number of hospitals in Boston, MA, Philadelphia, PA, and Toronto, Canada, between 1976 and 1980 (Rosenberg *et al.*, 1982). Controls were 712 children with other malformations, mainly of the gastrointestinal, musculoskeletal and central nervous systems. Mothers were interviewed in their homes within six months of delivery about consumption of a number of caffeine-containing beverages, including coffee, tea and cola. Consumption of coffee was 0, occasional, 1-2 or >3 cups per day. No association was found between coffee consumption and any of the six malformations [all RRs, $\leq$1.4]. Adjustment for a large number of potentially confounding variables — but not for alcohol consumption — in the analysis did not change these estimates. [The Working Group noted that the use of malformed infants as controls helps reduce recall bias, but it might be inadequate if caffeine were a teratogen that affects many sites.]

A monitoring system identified 755 children with birth defects in Finland between 1980 and 1982 (Kurppa *et al.*, 1983) including 112 with central nervous system defects, 241 with orofacial clefts, 210 with musculoskeletal defects and 143 with cardiovascular malformations. Thirty-five pairs that included habitual tea drinkers and 14 pairs with incomplete data were excluded. One control infant matched to each case was an infant whose birth immediately preceded that of the

case in the same maternity district. Information on coffee drinking was collected through interviews; cola drinking was infrequent. No important difference was seen between mothers of cases and of controls regarding the consumption of coffee during pregnancy. After adjustment for maternal age, smoking and alcohol consumption, the RR for coffee drinkers relative to those who did not drink coffee was 1.1 (95% confidence interval [CI], 0.8-1.3). Separate analyses of the four diagnostic categories showed no significant association.

As reported in an abstract, a case-control study of risk factors for cleft palate was carried out in five areas of Japan from 1978 to 1981. One control was matched to each of 194 cases for residence, sex, birth order and maternal age. Questionnaires answered by mothers included information on dietary habits. Frequent intake of coffee was associated with a RR of 2.3 ($p < 0.05$) (Tohnai *et al.*, 1984).

Furuhashi *et al.* (1985) carried out a prospective study in Japan in which 9921 women at 24 weeks' gestation or more were interviewed about coffee and tea drinking. Women were divided into five consumption groups: those who drank neither tea nor coffee, drinkers of fewer than five cups of coffee per day, five or more cups of coffee per day, coffee (any quantity) plus green tea, and green tea only. The rates of congenital anomalies of any type were 3.7% among coffee and/or tea drinkers and 1.7% among women who drank neither beverage. [The Working Group calculated that this difference was highly significant ($p < 0.001$), although the authors stated the opposite.] The association with coffee drinking was particularly strong for multiple anomalies. [The Working Group noted that no data are given on how the women were selected, or on when and where the study was carried out. Data on refusals and losses to follow-up are not given. Confounding variables were not adjusted for. It was surprising that the excess risk was seen for a wide variety of congenital malformations, including those associated with chromosomal anomalies.]

Tikkanen and Heinonen (1988) carried out a case-control study of maternal exposure to organic solvents and cardiovascular malformations in Finland in 1982-84. The 569 cases were identified from a population-based registry of congenital malformations; all diagnoses were confirmed by a cardiologist with experience in teratology. Controls were selected randomly from 52 hospitals in the country, and of 1200 controls selected, 1052 (88%) were included in the study. Mothers were interviewed at maternity welfare centres concerning exposures during the first trimester of pregnancy. Coffee drinkers were equally distributed among cases and controls: 82.3% and 81.8%, respectively.

Low birthweight and/or preterm delivery: The three best-designed studies are summarized in Table 30.

Table 30. Summary of selected[a] studies that provide relative risks (RR) for low birthweight in relation to coffee or caffeine intake of mothers

Reference, location and design	No. of women	Coffee or caffeine consumption	RR (95% CI[b])	Comments
van den Berg (1977) California, USA Prospective	8 514	≤1 cup/day 2–6 cups/day ≥7 cups/day	1.0 [1.4][c] [2.2][c]	Coffee intake
		≤6 cups/day ≥7 cups/day	1.0 1.2	RR adjusted for smoking $p = 0.01$, calculated by Hogue (1981)
Linn *et al.* (1982) Boston, USA Cross-sectional	12 205	< 4 cups/day ≥4 cups/day	1.0 1.2 (0.9–1.6)	Adjusted for smoking and other confounding variables Coffee intake
Martin & Bracken (1987) New Haven, USA Prospective	3 891	Nondrinkers 1–150 mg/day 151–300 mg/day > 300 mg/day	1.0 1.4 (0.7–3.0) 2.3 (1.1–5.2) 4.6 (2.0–10.5)	Term deliveries only; RR adjusted for race, parity, smoking and gestational age Caffeine intake

[a] Selected on the basis of design and quality
[b] CI, confidence interval
[c] Crude RR calculated by the Working Group

Mau and Netter (1974) carried out a prospective study of over 5200 pregnant women from 20 maternity departments in the Federal Republic of Germany. The women were interviewed during the first trimester of pregnancy, but little information was provided on how coffee drinking was quantified. Compared to nondrinkers, women who occasionally drank coffee had a RR of [1.4]; frequent drinkers had a RR of [1.6] for delivering a low birthweight (<2500 g) baby [(p < 0.01)]. The risk among drinkers remained unchanged after stratification for smoking (as reanalysed by Hogue, 1981).

van den Berg (1977) studied the effect of coffee consumption on birthweight and preterm delivery in a prospective study carried out in California, USA, between 1960 and 1967. Approximately 15 000 pregnant women receiving antenatal care under a prepaid medical plan were enrolled. Data were obtained from their medical records as well as from interviews covering reproductive history, socioeconomic factors, smoking habits and beverage consumption. A dose-response effect of coffee drinking was seen on low birthweight (see Table 30). A similar effect was noted on prematurity (gestational age under 37 weeks at birth), with RRs of [1.3] for women drinking two to six cups per day and [1.8] for those drinking seven or more cups, compared to women drinking up to one cup per day. Hogue (1981) examined the data on low birthweight after adjustment for smoking and length of gestation: a smaller but still significant RR of 1.2 was found for women who drank seven or more cups per day as compared to women who drank fewer than seven cups per day.

Arnandova and Kaculov (1978) reported a study of the pregnancy outcomes of 600 women in the USSR in 1976. Coffee consumption was not associated with prematurity, but the mean birthweight of infants born to coffee drinkers (usually one to two cups per day) was 115 g less than that of babies of women who did not drink coffee. The authors commented that this difference was probably due to greater consumption of alcohol and tobacco among coffee drinkers.

Kuzma and Sokol (1982) carried out a study of pregnant women who gave birth at four hospitals in California, USA, in 1974-78. About three-quarters of the women receiving antenatal care in these hospitals answered a self-administered questionnaire on their first visit, which included information on demographic and socioeconomic variables and on the use of coffee, alcohol, tobacco and other substances. If a mother had not sought antenatal care or had been missed in the enrollment procedure, the same data were obtained shortly after delivery; 37% of the study sample was recruited in this way. No important difference was found between information collected prospectively and retrospectively. Complete data were available for 5093 mother-infant pairs. After adjustment for gestational age, pre-pregnancy weight, weight gain, ethnicity and smoking, caffeine use was significantly (p < 0.01) associated with lower birthweight. [The Working Group

noted that it is not clear what percentage of eligible women were included in the study and that no information was given on how caffeine intake was calculated, particularly as to whether sources other than coffee were accounted for.]

In the study of Linn *et al.* (1982), described on p. 105, coffee drinking during the first trimester was associated in the crude analysis with a greater proportion of low birthweight. After adjustment for smoking, with or without other confounding variables, no significant effect of coffee drinking was seen: the RR for women drinking four or more cups a day was 1.2 (95% CI, 0.9-1.6) (see Table 30). No dose-response effect was present, and the association between coffee drinking and duration of gestation was nonsignificant.

In a case-control study, Berkowitz *et al.* (1982) compared 175 preterm infants and 313 term infants delivered at a Connecticut, USA, hospital in 1977. Preterm infants (cases) were defined as those born before 37 weeks of gestation, as determined by the Dubowitz criteria, and controls were a random sample of term infants. Interviews were completed with the mothers of 86% of potential cases and 95% of potential controls and included data on alcohol, smoking and on the average daily number of cups of coffee or tea taken during each trimester. Cases were of lower socioeconomic status than controls. Coffee drinking was not associated with shortened gestation period.

Watkinson and Fried (1985) investigated the possible association between coffee consumption during pregnancy and perinatal outcomes among women in the Ottawa area, Canada. From 1978, 371 women were studied for a range of perinatal outcomes. Five years later, in 1983, those women whose offspring were at least one year of age by that date were mailed a questionnaire concerning their consumption of coffee, tea, cola and other sources of caffeine throughout their pregnancies; 284 women (77%) responded. Coffee and tea samples were collected from 53 mothers and were used to estimate the caffeine content of these drinks. Caffeine consumption was greater among smokers and among women of low educational level. Caffeine intake, expressed as a continuous variable, was not significantly associated with birthweight or gestational age; however, the mean weight of babies born to 12 heavy users (> 300 mg caffeine/day) was 3158 g, compared to 3537 g for the remaining sample ($p < 0.05$). This association was still significant after adjustment for nicotine use but not quite significant ($p = 0.06$) after controlling for maternal education. No association was found between heavy use and gestational age. [The Working Group noted that women had been asked to recall the intake of a number of caffeine-containing substances several years after a pregnancy. No dose-response effect was present.]

In the study of Furuhashi *et al* (1985), described on p. 106, no significant difference in mean birthweight was seen between the five categories. Infants born to 53 women who drank five or more cups of coffee per day, however, were on average

about 70 g lighter than the other infants. The incidence of infants who were small for gestational age was approximately three times greater [$p < 0.05$; Poisson test] in the women who drank more than five cups of coffee per day. [The Working Group noted that no information on smoking was available, and no definition was given of 'small for gestational age'.]

Martin and Bracken (1987) carried out a prospective study of 3891 pregnant women receiving antenatal care in greater New Haven, Connecticut, USA, between 1980 and 1982. A total of 6219 women were considered for the study but only 5331 agreed to be contacted. Of these, 4926 fulfilled the entry criteria, and 85% were interviewed at home within a few weeks of the first prenatal visit. Caffeine consumption during pregnancy was estimated from data on the consumption of coffee, tea, colas and drugs. Data on pregnancy outcomes were obtained from hospital records and were analysed using logistic regression. Caffeine consumption was associated with lower socioeconomic status, smoking and alcohol intake. The effect of caffeine on birthweight was restricted to term infants. After adjustment for gestational age, race, parity and smoking, intake of caffeine at >300 mg/day was associated with a RR of 4.6 (95% CI, 2.0-10.5) for low birthweight compared with that of women who did not consume caffeine-containing beverages or drugs. A dose-response pattern was present (see Table 30). No association was seen between caffeine intake and gestational age.

Brooke *et al.* (1989) studied the effects on birthweight of smoking, alcohol, caffeine, socioeconomic factors and psychosocial stress among 1860 white women in London, UK, of whom 1513 were included in the study and interviewed prenatally. Birthweight was corrected for gestational age, maternal height, parity and baby's sex (adjusted to a standard population). Smoking was found to be the most important single factor, inducing a 5% reduction in birthweight, which was statistically significant even when corrected for consumption of alcohol, tea, coffee or caffeine. Total caffeine consumption (milligrams per week) was calculated for the entire pregnancy and was found to be related to birthweight (adjusted to 40 weeks): with an intake of 0-200 mg/day, birth weight was 3664 g; with 200-400 mg/day, birthweight was 3609 g; and with a daily intake of more than 400 mg/day, the average birthweight was 3556 g. The corresponding birthweight ratios were 1.050, 1.034 and 1.019. In a crude analysis (not corrected for smoking), the difference across groups gives $p = 0.005$; however, when corrected for smoking, the adjusted birthweight ratios did not differ with caffeine consumption categories, being 1.051 (95% CI, 1.039-1.062) for 0-200 mg/day, 1.055 (95% CI, 1.043-1.068) for 200-400 mg/day and 1.054 (95% CI, 1.033-1.075) for >400 mg/day. The authors concluded that smoking was the main environmental cause of variations in birthweight (corrected for gestational age). [The Working Group noted that the

study was not designed to detect a possible effect on birthweight mediated through prematurity.]

In Costa Rica, women of low socioeconomic status were contacted at an antenatal care service before they were six months' pregnant (Muñoz *et al.*, 1988). Of 378 women contacted, 301 fulfilled the entry criteria, which included being aged between 17 and 30 years, uncomplicated pregnancy and delivery, term delivery, avoidance of smoking and alcohol, and initiation of breastfeeding. The study was restricted to non-coffee drinkers and to women who drank 450 ml or more coffee per day. Of 110 eligible women, 62 (56%) dropped out, so that the study was limited to 22 coffee drinkers and 26 who did not drink coffee. Dropouts had had less education and higher parity than the women studied. Birthweight was 121 g lower for the children of coffee drinkers than those of non-coffee drinkers ($p < 0.001$). This difference was still significant after adjustment for potential confounding factors through multiple linear regression. Iron deficiency anaemia was found in 23% of the coffee consumers and in none of the non-consumers. The haematocrit levels of infants of coffee-drinking mothers at one week and one month of age were lower than those of the controls. This association persisted after adjustment for confounding factors. [The Working Group noted the high rate of dropouts.]

The effect of first-trimester maternal caffeine consumption on birthweight was examined in a case-control study of 131 cases and 136 controls (Caan & Goldhaber, 1989). Heavy consumption of caffeine (300 mg/day or three servings) from coffee, tea or cola drinks was associated with a high prevalence of low birthweight. For women who had drunk three or more cups of coffee per day, the crude odds ratio was 2.1; when adjusted for ethnicity, alcohol, cigarettes, pre-pregnancy weight, weight gain and parity, the odds ratio increased to 2.8 (95% CI; 0.89-8.7).

Spontaneous abortions and stillbirths: In the study of Arnandova and Kaculov (1978), described on p. 108, no difference was reported in the rates of spontaneous abortions and stillbirths in relation to coffee drinking.

In the study of Furuhashi *et al.* (1985), described on p. 106, 2% of pregnant women who had drunk coffee and 1.2% of controls had spontaneous abortions ($p < 0.001$). [Reservations regarding this study are given on p. 106. The Working Group noted further that most abortions are likely to have been missed in this study, since women were recruited at 24 weeks' gestation or more. It is unclear whether stillbirths were included among abortions since there was no mention of stillbirths in the report. No confounding variable was adjusted for.]

Srisuphan and Bracken (1986) carried out a prospective study of 3135 pregnant women who had sought antenatal care in the New Haven, Connecticut, area, USA, between 1980 and 1982. Details of the study design are given on p. 110 in the description of the study by Martin and Bracken (1987). The abortion rates were 1.8% for non-caffeine users, 1.8% for light users (1-150 mg/day) and 3.1% for

moderate-to-heavy users (> 150 mg/day) (trend not significant). Comparing moderate-to-heavy users with the remainder, the RR was 1.7 (95% CI, 1.0-2.7; p = 0.03). This estimate was unchanged (RR, 1.7; p = 0.03) after adjustment for maternal age, gestational age, Jewish religion, prior gynaecological surgery and previous spontaneous abortions. Women who received caffeine only from coffee appeared to have a higher risk of miscarriage (RR, 2) than those who drank only tea (1.1) or colas (1.3), but the numbers were small and the differences not significant.

Kršnjavi and Mimica (1987) studied 308 pregnant women in Zagreb, Yugoslavia, in 1982-83, of whom 246 (80%) responded to a questionnaire on alcohol, tobacco and coffee consumption. No association was found between coffee drinking and the frequency of spontaneous abortions.

Effects on fertility: Information on caffeine consumption before trying to conceive was obtained for 221 women. The adjusted mean fecundability ratio for higher caffeine users compared to non-users was 0.80 (Wilcox *et al.*, 1988). An association between reduced fertility and caffeine intake received further support from data presented in a letter to the Editor of *The Lancet* (Christianson *et al.*, 1989). In a further study, however, no association was found between time to conceive and coffee consumption among 2817 women who had recently had a liveborn child, while there was a suggested effect of tea and also of age and tobacco smoking (Joesoef *et al.*, 1990).

(iii) *Genetic and related effects*

The nonpolar fractions of urine from humans who had ingested 12 g of instant coffee per day for four days or 12 g within 2 h were not mutagenic to *S. typhimurium* TA98 or TA100 in the presence or absence of an exogenous metabolic system, with or without β-glucuronidase treatment of the urine (Aeschbacher & Chappuis, 1981).

Organic fractions isolated from the urine of drinkers of at least five cups of coffee per day induced chromosomal aberrations in cultured Chinese hamster ovary cells. This clastogenic effect was abolished in two of the organic fractions by the addition of either catalase or superoxide dismutase to the cell system, suggesting that active oxygen species are involved (Dunn & Curtis, 1985).

In a population of 30 smokers and 30 nonsmokers, a positive, statistically significant linear relationship between the square-root transformed frequency of sister chromatid exchange in cultured peripheral blood lymphocytes and coffee consumption was reported (Reidy *et al.*, 1988). In the same population, a positive linear relationship was observed between the average number of cups of coffee consumed per day and the proportion of low-folate cultured blood lymphocytes with chromosomal aberrations. Only about 5% of the variance was attributable to

coffee consumption. In comparison, smoking contributed about 10% and the use of two different slide scorers contributed about 15% (Chen *et al.*, 1989). [The Working Group noted that this study of smokers and nonsmokers was not designed to evaluate coffee consumption.]

In a study on 44 otherwise healthy splenectomized persons, drinking coffee (and occasionally tea) was associated with a significant, dose-dependent increase in the frequency of micronuclei in both reticulocytes and mature erythrocytes (Smith *et al.*, 1990).

3.3 Epidemiological studies of carcinogenicity to humans[1]

(*a*) *Descriptive epidemiology*

These studies are of four main types. Ecological studies examining geographic variation in coffee consumption and either cancer incidence or mortality rates (Takahashi, 1964; Stocks, 1970; Shennan, 1973; Armstrong & Doll, 1975; Binstock *et al.*, 1983; Decarli & La Vecchia, 1986; Phelps & Phelps, 1988) are the most common. A second type of study examines time trends in cancer rates and coffee consumption within a given country or countries (Morrison, 1978; Pannelli *et al.*, 1989). A hybrid design combines an examination of time trends (Cuckle & Kinlen, 1981; Benarde & Weiss, 1982) and geographic differences among countries. The final type of descriptive studies examines cancer rates among special population groups such as Mormons, a cultural group one of whose practices is abstension from tea and coffee drinking (Enstrom, 1975; Lyon *et al.*, 1976; Enstrom, 1978, 1980; Lyon *et al.*, 1980), in which incidence and mortality rates for different cancer sites were compared either with the general population or with non-practising Mormons. It is not possible in these studies, however, to distinguish between the effect of reduced coffee and tea consumption, reduced cigarette smoking and alcohol drinking and the other prohibited behaviours of this sect; they do not contribute to our knowledge of the association between coffee drinking and cancer risk and are not discussed further in this monograph.

(i) *Bladder cancer*

In an examination of time trends in incidence rates and per-caput coffee imports in the USA and Denmark, coffee consumption was adjusted for cigarette consumption. No association was noted between changes in bladder cancer rates

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[1]The Working Group was aware of a large multicentre case-control study on pancreatic cancer which has been completed, but the results were not available.

and coffee imports in Denmark or among women in the USA; a weak positive association was noted for US men (Morrison, 1978). Cohort and period variation in bladder cancer mortality in Italy between 1950-54 and 1980-81 was compared with changes in coffee, cocoa, tea and cigarette consumption. The authors stated that changes in coffee intake do not explain the cohort changes (Pannelli *et al.*, 1989). No association was noted in the study of either Armstrong and Doll (1975) or Stocks (1970).

(ii) *Breast cancer*

Weak positive correlations were reported between incidence ($r = 0.42$) and mortality ($r = 0.37$) from breast cancer and coffee consumption in a geographical study (Armstrong & Doll, 1975). Phelps and Phelps (1988) conducted an ecological study, which did not distinguish between tea and coffee consumption, and reported a correlation of 0.004 with breast cancer mortality ratios after adjusting for dietary fat intake.

(iii) *Endometrial cancer*

A positive correlation was reported between the incidence of corpus uterine cancer ($r = 0.43$) and international variation in coffee consumption (Armstrong & Doll, 1975).

(iv) *Kidney cancer*

The correlation between age-adjusted mortality rates from kidney cancer in 1964 and per-caput coffee consumption was 0.79 ($p < 0.001$) (Shennan, 1973). A reported correlation between coffee consumption and the incidence of kidney cancer (men, 0.62; women, 0.40) was explained by the stronger association with consumption of animal protein (Armstrong & Doll, 1975), which is also correlated with coffee consumption.

(v) *Leukaemia*

A positive correlation was reported between mean, age-adjusted mortality rates for leukaemia in 1964-65 and annual coffee consumption (males, $p = 0.001$; females, $p = 0.03$) (Stocks, 1970).

(vi) *Ovarian cancer*

A positive correlation was reported between mean, age-adjusted mortality rates in 1964-65 and annual coffee consumption ($p = 0.006$) (Stocks, 1970). A weak correlation was reported between incidence ($r = 0.50$) and mortality ($r = 0.50$) and coffee consumption in the study of Armstrong and Doll (1975).

(vii) *Pancreatic cancer*

An association was reported between mean, age-adjusted death rates for males in 1964-65 and annual coffee consumption ($p = 0.008$) (Stocks, 1970). An

examination of international time trends in mortality rates and coffee consumption, in which adjustment was made for changes in lung cancer mortality as a proxy for smoking, showed correlations of 0.58 (males) and 0.66 (females) (Cuckle & Kinlen, 1981). An additional correlation study in the USA, which used lag periods to examine trends in mortality ratios and coffee consumption, reported correlation coefficients ranging from 0.39 to 0.68 over the period of the study (Benarde & Weiss, 1982). A simple correlation coefficient of 0.59 ($p = 0.001$) between coffee consumption in 1957-65 and mortality in 1971-74 was found to be significant after controlling for confounding variables (Binstock *et al.*, 1983). Positive but nonsignificant correlation coefficients have been reported between age-standardized, sex-specific mortality rates and per-caput coffee consumption in 20 regions of Italy (Decarli & La Vecchia, 1986).

(viii) *Prostatic cancer*

The correlation between age-adjusted mortality ratios for 1956-59 and per-caput coffee consumption for 1955-59 was 0.7 ($p < 0.001$) (Takahashi, 1964). This association was confirmed using mortality data for 1964-65 ($p < 0.001$) (Stocks, 1970).

(*b*) *Cohort studies*

The association between coffee consumption and subsequent cancer incidence or mortality has been investigated in a number of prospective studies. In the following text, the most recent publication on cancer outcomes has been summarized when a number of papers have been generated from a single cohort study. The studies are summarized in Table 31 on p. 119.

(i) *All sites combined*

Heyden *et al.* (1979) conducted a nine-year follow-up of 2530 US men and women interviewed about their daily coffee consumption in 1967-69. Seventy-four cancer deaths with biopsy or hospital data were analysed. Two sets of controls consisted of age-, race- and sex-matched deaths from cardiovascular disease and live study participants. Coffee consumption was more common among each set of controls than among the cancer cases (odds ratio, 0.67; $p > 0.05$). The matched-pairs odds ratios were based on 6:9 discordant pairs for each set of controls.

The association between coffee consumption and mortality from all causes, coronary heart disease and noncoronary causes over 19 years was examined among 1910 white men, aged 40-56 at the time of the baseline examination, who took part in a study of the Chicago Western Electric Company (LeGrady *et al.*, 1987). Intake was measured in terms of 6-oz (178-ml) cups over 28 days. Since only 97 men consumed

two or more cups of decaffeinated coffee per day, intake of caffeinated and decaffeinated coffee was combined. The Cox proportional hazards model was used to analyse the association between coffee intake and mortality after adjustment for age, diastolic blood pressure, serum cholesterol and smoking. The adjusted RR for cancers at all sites comparing none to one cup per day with all other levels of intake was 1.6 (95% CI, 0.95-2.6). [The Working Group noted that no analysis of site-specific cancer risks was undertaken.]

(ii) *Site-specific analyses*

A case-control analysis of a cohort study investigated pancreatic cancer mortality in a 16-50-year follow up of 50 000 male former college students (Whittemore *et al.*, 1983). There were 126 deaths from pancreatic cancer. Data on coffee and tea consumption and other variables had been collected during a physical examination at college. No significant association was noted with coffee consumption.

A series of letters to the Editor of *The Lancet* (Nomura *et al.*, 1981; Kinlen *et al.*, 1984; Nomura *et al.*, 1984) report pancreatic cancer incidence in cohort studies. Since Nomura *et al.* (1986) reported on pancreatic cancer and coffee consumption in the same cohort, no additional data from these letters are reported here. Kinlen *et al.* (1984) carried out a cohort study of 14 085 men in London, UK. There were 47 deaths from pancreatic cancer, identified from death certificates, in the 13 years of follow-up to 1982. The mean daily consumption of coffee, adjusted for age and smoking, was 0.83 cup for cases and 1.00 cup for controls.

In a Hawaiian cohort study of the association between cancer incidence and coffee consumption, 7355 Japanese men were followed for a minimum of 14 years from the time of collection of 24-h consumption data in 1965-68 (Nomura *et al.*, 1986). There were 672 incident cancers in the cohort as of July 1983. Incidence rates were adjusted for age or both age and smoking, using the entire cohort as the standard population. The reference category for all analyses included the 1173 men who reported drinking no coffee. Coffee intake was analysed according to none, one to two, three to four and five or more cups per day. No significant association was reported between coffee drinking and age- and smoking-adjusted RRs for pancreatic cancer (p for trend, 0.41), lung cancer (p for trend, 0.19) or bladder cancer (p for trend, 0.25). No association was noted with colon cancer risk. [The Working Group noted that dietary information was based on a single 24-h recall.]

A series of papers has examined the association between coffee intake and 21-year mortality among Seventh-day Adventists in the USA (Phillips & Snowdon, 1983; Snowdon & Phillips, 1984; Phillips & Snowdon, 1985).

The final analysis in the series was based on a cohort of 25 493 subjects (Phillips & Snowdon, 1985). Univariate analyses indicated a consistent positive

relationship between colon and rectal cancer death rates and increased coffee consumption for both men and women. Drinking two or more cups of coffee per day was associated with a crude RR for colon cancer of 2.0 (95% CI, 1.1-3.6) for men and 1.5 (0.8-2.6) for women. Different multivariate analyses were completed for the first 10 and the last 11 years of follow-up since the association between coffee drinking and colorectal cancer varied across this period. The excess risk associated with drinking two or more cups of coffee per day in the latter follow-up period was 3.0 ($p > 0.05$) for men following adjustment for age, egg consumption, excess weight and meat consumption. The equivalent adjusted risk for women was 2.4 ($p < 0.05$). [The Working Group noted that the distribution of coffee drinking in this population is unusual because there are few heavy coffee drinkers: 17-18% of the population drank two or more cups per day. There may be residual confounding by other factors associated with non-adherence to dietary restrictions.]

Two papers have been published from a prospective study conducted in Norway examining the relationship between coffee drinking and cancer incidence and mortality among approximately 16 000 men and women (Heuch *et al.*, 1983; Jacobsen *et al.*, 1986). Site-specific incidence and mortality were determined among three groups of people: a probability sample of adult males selected from the 1960 census, Norwegian brothers of migrants to the USA, and spouses and siblings of people interviewed for a case-control study of gastrointestinal cancer. Average daily coffee consumption was determined by questionnaire in 1967-69. No data are presented on the completeness of the 11.5-year follow-up, during which time there were 602 cancer deaths and 1498 incident cancers (including 207 nonmelanomatous skin cancers). Incidence data that were presented for approximately 20 cancer sites were adjusted for sex, age and residence; some additional analyses among males were also adjusted for smoking. In the calculation of RRs, comparisons were made between the consumption of two or fewer and seven or more cups per day. The RR for mortality from cancers at all sites was 1.3 (p for trend = 0.09). Raised RRs were reported for the incidence of cervical (10.6; p for trend = 0.07) and lung cancer (1.8; p for trend = 0.02); the smoking-adjusted RR for lung cancer incidence among males was 1.1 (p for trend = 0.84). Heavy coffee drinking was associated with reduced risks for the incidence of colon (RR, 0.6; p for trend = 0.10) and kidney cancer (RR, 0.3; p for trend = 0.01). The RR for the incidence of pancreatic cancer was 0.7 (p for trend = 0.37) and that for bladder cancer was 0.99 (p for trend = 0.99). [The Working Group noted that odds ratios were in fact calculated and presented as RRs.]

A cohort study investigated a six-year follow-up of pancreatic cancer incidence among 122 894 men and women who had completed a questionnaire collecting data on coffee, tea, smoking and alcohol use in 1978-84 (Hiatt *et al.*, 1988). There were 49 cases of pancreatic cancer. A multivariate analysis (adjusting for age, sex, ethnicity,

blood glucose level, smoking, alcohol and diabetes) identified no increased risk associated with increasing coffee consumption.

A cohort study (Mills *et al.*, 1988) of approximately 34 000 non-Hispanic, white Californian Seventh-day Adventists followed participants for six years after their completion of a questionnaire determining their exposures in 1976. Forty deaths from pancreatic cancer were reported. In the analyses of age- and sex-adjusted RRs for pancreatic cancer, current consumption of coffee at least once a day relative to no consumption was associated with a RR of 2.0 (95% CI, 0.9-4.4). Past consumption showed an inconsistent, nonsignificant protective relationship with mortality from pancreatic cancer. Multivariate analyses, using the Cox proportional hazards model, give a RR for current coffee consumption, adjusted for age, sex and smoking of 2.2 (95% CI, 0.6-8.0).

A cohort study of colorectal cancer incidence in a retirement community (Wu *et al.*, 1987) identified 58 male and 68 female cases among 11 888 people in a 4.5-year follow up. Questionnaires were completed between 1981 and 1982 by 62% of community members. In an analysis that adjusted only for age, there was no effect of increased coffee intake on cancer risk in women and a nonsignificant increase in men.

Paffenbarger *et al.* (1978) examined the association between coffee drinking and mortality from six cancers in a nested case-control analysis of a cohort study in the USA of 50 000 male former college students (the same population as used by Whittemore *et al.*, 1983, p. 116). Each case was matched with four controls chosen randomly from among classmates born in the same year and known to have survived the decedent. Information on risk factors was obtained from medical records completed at the time of college entry. Coffee drinking at that time was associated with a two- to three-fold higher risk for Hodgkin's disease, lymphatic and myeloid leukaemia, but no significant association was found with non-Hodgkin's lymphoma, with malignant melanoma or with other and unspecified leukaemias.

(c) *Case-control studies*

(i) *Bladder and urinary tract*

Bladder cancer: More than two dozen case-control studies have been published on the association between coffee and bladder cancer. Their main results are summarized in Tables 32 (users *versus* non-users) and 33 (dose-response relationships and significance of the linear trend in risk) on pp. 129 and 132. Whenever possible, combined RRs are derived from data presented in strata of sex, age, race and other possible covariates.

Cole (1971) reported a population-based case-control study of 445 cases of cancer of the lower urinary tract (renal pelvis, ureter, bladder (90% of cases) and

Table 31. Summary of results of cohort studies on cancer and coffee consumption

Reference, location and site	Subjects	Events (deaths or cases)	Coffee consumption (cups/day)	RR (95% CI)	Comments
Heyden *et al.* (1979) USA All sites	2530 men and women	74	<5 ≥5	1.0 0.7	$p > 0.05$; same RR with each control group
LeGrady *et al.* (1987) USA All sites	1910 white men	117	0–1 ≥2	1.0 1.6 (0.95–2.6)	Adjusted for age, diastolic blood pressure, serum cholesterol and smoking
Whittemore *et al.* (1983) USA Pancreas	50 000 men	126	0 Any	1.0 1.1 (0.7–1.9)	Past coffee consumption Adjusted for age, college and class year
Kinlen *et al.* (1984) UK Pancreas	14 085 men	47	Mean: cases, 0.83 controls, 1.00		Adjusted for age and smoking
Nomura *et al.* (1986) Hawaii	7355 Japanese men				
Pancreas		21	0 1–2 3–4 ≥5	1.0 [1.2] [2.1] [1.6]	$p = 0.41$, adjusted for age and smoking
Lung		110	0 1–2 3–4 ≥5	1.0 1.1 1.1 1.4	$p = 0.19$, adjusted for age and smoking
Bladder		39	0 1–2 3–4 ≥5	1.0 1.0 1.4 1.6	$p = 0.25$, adjusted for age and smoking

Table 31 (contd)

Reference, location and site	Subjects	Events (deaths or cases)	Coffee consumption (cups/day)	RR (95% CI)	Comments
Phillips & Snowdon (1985) USA Colon	Seventh-day Adventists 9 175 men	53	< 1 1 ≥2	1 1.3 (0.5–3.4) 2.0 (1.1–3.6)	p = 0.04, adjusted for age
	16 336 women	83	< 1 1 ≥2	1 1.2 (0.6–2.4) 1.5 (0.8–2.6)	p = 0.20, adjusted for age
Rectum	25 493 men and women	28	< 1 1 ≥2	1.0 1.4 (0.6–3.1)	p = 0.38, adjusted for age and sex
Wu *et al.* (1987) USA Colon and rectum	11 888 men and women	58 men	0–1 2–3 ≥4	1.0 1.3 (0.7–2.5) 1.5 (0.6–3.7)	Adjusted for age
		68 women	0–1 2–3 ≥4	1.0 1.5 (0.8–2.7) 1.2 (0.4–3.1)	
Hiatt *et al.* (1988) USA Pancreas	122 894 men and women	49	0 < 1 1–3 ≥4	1.0 0.8 (0.3–2.6) 0.9 (0.4–2.1) 0.7 (0.2–1.9)	Adjusted for age, sex, ethnic group, blood glucose, smoking, alcohol and diabetes
Mills *et al.* (1988) USA Pancreas	34 198 white male and female Seventh-day Adventists	40	Current use Never < Daily Daily	 1.0 1.4 (0.6–3.6) 2.0 (0.9–4.4)	p for trend = 0.087, adjusted for age and sex

Table 31 (contd)

Reference, location and site	Subjects	Events (deaths or cases)	Coffee consumption (cups/day)	RR (95% CI)	Comments
Mills *et al.* (1988) USA Pancreas (contd)			Past use Never < Daily Daily	 1.0 0.7 (0.2–1.9) 0.7 (0.3–1.5)	$p = 0.254$, adjusted for age and sex
Paffenbarger *et al.* (1978) USA	50 000 men				
Hodgkin's disease		45	Never Ever	1.0 2.5	$p = 0.07$; RR based on matched analysis
Non-Hodgkin's lymphoma		89	Never Ever	1.0 1.6	Nonsignificant
Malignant melanoma		45	Never Ever	1.0 1.3	Nonsignificant
Lymphatic leukaemia		27	Never Ever	1.0 2.7	$p = 0.06$
Myeloid leukaemia		41	Never Ever	1.0 3.2	$p = 0.02$
Other/unspecified leukaemias		30	Never Ever	1.0 0.8	Nonsignificant

urethra) and 451 controls from Massachusetts, USA. The study, in which 90% of cases and controls participated, found a RR of 1.2 for men and 2.6 for women among coffee drinkers *versus* non-coffee drinkers, after adjustment for age and smoking at three levels (non-smokers, $\leq$1/2 pack, > 1/2 pack per day). The RR was significant for women, and was 1.6 for one, 3.8 for two to three and 2.2 for four or more cups per day. The association was apparently stronger among the 90 cases who neither smoked nor had a high-risk occupation.

In a study conducted in Louisiana, USA, Dunham *et al.* (1968) obtained information on 493 patients with bladder cancer and 527 controls admitted to hospital for a wide spectrum of other conditions. The data were stratified for type of coffee, sex and race, and reanalysed by Fraumeni *et al.* (1971), in a study reported as a letter to the Editor of *The Lancet*. Some association was found for blacks (significant in females) but not for whites. After adjustment for age and smoking, the overall RR was 1.5 (nonsignificant). There was no consistent dose-response relationship.

In a Canadian case-control study of 158 men and 74 women with bladder cancer and similar numbers of controls with benign prostatic hypertrophy (men) or stress incontinence (women), data were collected using a postal questionnaire on previous health, employment, beverage and artificial sweetener intake (Morgan & Jain, 1974). The overall response rate was 69% among the cases and 57% among the controls, but the numbers of subjects included in the final analysis were further reduced by matching for age. The mean number of cups of coffee drunk per day was 1.8 for cases and 2.0 for controls among females, and 2.1 for both cases and controls among males. The RR (calculated by the Working Group) for coffee drinkers *versus* non-drinkers was [0.7] for males and [1.3] for females. None of these estimates, nor the corresponding trends in risk with dose was significant.

A study by Simon *et al.* (1975) was based on 216 white female cases of cancer of the lower urinary tract (renal pelvis, ureter, bladder (95% of cases) and urethra) identified at 10 hospitals in urban areas in Massachussets, USA. Among them, 40 had died and 41 did not respond. The remaining 135 cases were compared with 390 respondent controls out of a total of 648 selected from the discharge lists of the same hospitals. Postal questionnaires were used for data collection. Ninety-three percent of cases drank coffee *versus* 85% of the controls, with an unadjusted RR of 2.1 (95% CI, 1.1-4.3). The unadjusted RRs were 2.2 for one or two cups per day, 1.9 for three to four and 2.3 for five or more. [Adjustment for smoking by the Working Group was possible according to two categories only (nonsmokers and light smokers *versus* moderate to heavy smokers); the RR declined to [1.9] and was no longer significant.]

Wynder and Goldsmith (1977) utilized data collected between 1969 and 1974 on patients interviewed in 17 hospitals in six areas of the USA (46% from Memorial

Hospital in New York City). A total of 574 male and 158 female bladder cancer patients and equal numbers of hospital controls were considered. The refusal or nonparticipation rate was less than 4%. The RRs for whether coffee was ever drunk or not, adjusted for smoking at four levels, were above unity [RR, 1.5 for males, 1.3 for females]. Trends in risk with dose were not significant.

Miller *et al.* (1978) published data from a study originally planned to consider the possible association between isonicotinic acid hydrazide, a drug used in the treatment and prophylaxis of tuberculosis, and bladder cancer. Patients admitted to a hospital in Ottawa for bladder cancer (255 cases) and other urological conditions (510 controls) completed a questionnaire including, among other items, information on coffee and tea consumption. In relation to coffee, a matched, unadjusted analysis provided a RR of 1.3 for males and of 1.6 for females. [The Working Group noted that no information was provided on the confounding or modifying effect of covariates, including smoking.]

Mettlin and Graham (1979) studied the role of dietary factors in the risk for bladder cancer using data from the Roswell Park Memorial Institute, NY, USA, collected between 1957 and 1965 (Bross & Tidings, 1973). A total of 429 white male and 140 white female patients with primary bladder cancer were compared with 1025 controls admitted for non-neoplastic conditions. After adjustment for smoking in two categories (less than half a pack *versus* half a pack or more per day), the RR for five subsequent levels of coffee drinking was around unity in women, but above unity in men, in the absence, however, of any trend in risk (RRs, 1 (referent), 1.4, 1.2, 2.1 and 1.6). Consequently, in the two sexes combined, there was a small, inconsistent increase in smoking-adjusted RRs for bladder cancer risk with increasing coffee consumption: 1 (referent), [1.2, 1.1, 1.8 and 1.3].

Howe *et al.* (1980) reconsidered the relation between coffee and bladder cancer in a Canadian population-based case-control study of 480 male and 152 female case-control pairs (Miller, 1977). The overall response rate was 77% for the cases and 86% for the controls. For users *versus* non-users of any coffee preparation, the RR was 1.4 for men and 1.0 for women, neither estimate being significant. The unadjusted RRs were 1.5 (95% CI, 1.0-2.2) for men consuming brewed coffee and 1.5 (1.1-2.0) for those drinking instant coffee, and 1.4 (0.8-2.6) for women consuming instant coffee, but no dose-response relationship was found.

Cartwright *et al.* (1981) conducted a case-control study of bladder cancer in West Yorkshire, UK, a high incidence area for the disease. The study population included 841 cases (631 male, 210 female; 622 prevalent, 219 incident) and 1060 hospital patients of similar age and same sex. In this preliminary report, no information was given on participation rate. Questions were asked on coffee drinking habits and various types of coffee, besides other known and potential bladder cancer risk factors (smoking, saccharin use, occupational history, past

medical history). No relation was found between any type of coffee consumption and bladder cancer risk after adjustment for smoking. The RRs for drinking all types of coffee, adjusted for age, type of case (incident/prevalent) and cigarette smoking, were 1.1 for males and 0.8 for females (corresponding estimates not adjusted for smoking were 1.3 and 1.1, respectively). Similarly, no heterogeneity in risk was observed between instant and ground coffee. The authors concluded that the correlation between cigarette and coffee consumption can explain the moderate association observed in the unadjusted analysis.

Morrison *et al.* (1982) published data from a population-based case-control study from Boston, MA, USA (587 cases, 528 controls), Manchester, UK (541 cases, 725 controls) and Nagoya, Japan (289 cases, 586 controls). A further report of a section of this study was made by Ohno *et al.* (1985). Controls were selected from electoral rolls or other population registries. Participation rates in various centres were over 80% for both cases and controls. The overall RR for coffee drinkers *versus* non-drinkers, adjusted for age, sex, centre and smoking was 1.0 (95% CI, 0.8-1.2), and in none of the centres was there consistent evidence of a dose-response relationship.

Najem *et al.* (1982) considered several risk factors for bladder carcinogenesis in a case-control study in New Jersey, USA, of 75 histologically confirmed cases among white people and 142 matched controls derived from the same clinic and hospital populations from which bladder cancer cases were obtained. Only five cases and 16 controls did not consume coffee. The RR (not adjusted) was 1.8, with a very wide 95% CI (0.1-10.0). [The Working Group noted the small number of cases and the limited information provided.]

Sullivan (1982) analysed 82 bladder cancer cases (out of 101 diagnosed) and 169 controls selected through random digit dialling in the area of greater New Orleans, LA, USA. In relation to coffee drinking, a number of inconsistent relationships was observed. White male cases, for instance, reported significantly greater consumption of brewed ground coffee than controls, and white women consumed more decaffeinated ground coffee than controls. No relationship was found with duration of use. [The Working Group noted that no RR was given, and there was no indication that adjustment was made for covariates.]

The largest case-control study on bladder cancer was that published by Hartge *et al.* (1983), based on 2982 cases and 5782 general population controls interviewed in a collaborative, population-based study conducted in ten geographical areas of the USA. A report of part of this study was made by Marrett *et al.* (1983). Participation was 73% for the cases and 82% for the controls. The RRs for ever *versus* never coffee drinking were 1.6 (95% CI, 1.2-2.2) for men, 1.2 (0.8-1.7) for women and 1.4 (1.1-1.8) for men and women combined, after simultaneous allowance for sex (when appropriate), age, race, geographical area and tobacco

consumption. When various levels of coffee consumption were considered, the RR was significantly above unity (1.5; 1.1-1.9) only for men drinking over 63 cups of coffee per week, but no dose-response relationship was evident for either men or women. Similarly, there was no association with duration of coffee drinking. No interaction was observed with geographical area, race, occupation, artificial sweetener use or history of urinary infections. The authors noted that adjustment for smoking reduced the RR for ever/never coffee drinking from 1.8 to 1.4, and that residual confounding by tobacco (or possibly other correlates of coffee drinking) may explain the persistent but inconsistent relation between bladder cancer and coffee. Men who drank only decaffeinated coffee (ground or instant) had an estimated RR of 1.2 (0.8-1.9) compared to men who never drank coffee. The corresponding estimate for women was 1.5 (0.9-2.6). Kantor *et al.* (1988), examining the same data set by three separate histological types (squamous-cell, adeno- and transitional-cell carcinomas), found a significant trend in risk for adenocarcinomas in men and women combined, although the number was extremely low (32 cases) and none of the point estimates was significant. [The Working Group noted that the lack of significance may be the result of less precise adjustment for smoking than in the study by Hartge *et al.* (1983).]

In a population-based study carried out using the Connecticut (USA) Tumor Registry during 1978-79, Marrett *et al.* (1983) investigated the relationship between coffee consumption and bladder cancer. Data were available on 412 cases aged 21-84 (80% of those identified) and 493 controls (81% of those selected). After adjustment for age and smoking, the RR for one cup per week or more was 1.3 for males and 1.1 for females; for more than seven cups per week the RR was 1.5 for males and [1.0] for females. In males, there was some evidence of a dose-response relationship: for over 21 cups per week, the RR was 2.0. No trend in risk with dose was evident in females, nor with duration in people of either sex. The authors noted that among male and female nonsmokers combined, the RR for more than seven cups per week was 1.9 (95% CI, 1.0-3.6). There was no significant effect of the consumption of decaffeinated coffee. [The Working Group noted that there may be some overlap between this study and that of Hartge *et al.* (1983).]

In a case-control study in Aarhus, Denmark, Mommsen *et al.* (1983a,b) collected information from cases admitted to hospital and (through mailed questionnaires) from population controls (response rate of first selected controls, 85%). The overall report, based on 165 male and 47 female cases, found no association with coffee drinking, but an elevated risk was observed (RR, 2.6) among women, although the estimate was not significant and only one case and five controls were not coffee drinkers. Dose-response relationships were not analysed. [The Working Group noted the small number of cases and the limited information provided.]

In a study in Greece, Rebelakos *et al.* (1985) compared 300 cases of histologically confirmed bladder cancer (250 male, 50 female) admitted to the major cancer hospital in Athens with an equal number of age- and sex-matched orthopaedic controls. The refusal rate was only approximately 1%. The RR, adjusted for smoking, was not elevated in drinkers of one cup per day compared with non-coffee users; however, a significant RR of 1.7 was found when drinkers of two or more cups were compared with those drinking fewer than two cups per day. For male and female cases combined, the point estimates for five levels of coffee consumption were 1 (referent), 1.2, 1.7, 2.7 and 0.7, and the trend in risk was significant ($p = 0.02$).

Gonzáles *et al.* (1985) reported a hospital-based case-control study in Spain based on 58 cases; two age-matched controls were available for each case — one with non-urinary tract cancer (excluding lung cancer) and one with non-neoplastic conditions. They found a RR of [0.6] (not significant) for 'habitual coffee consumers'. [The Working Group noted the small number of cases, the limited information provided and that no allowance was made for potential confounders.]

Jensen *et al.* (1986) conducted a population-based case-control study in 1979-81 in Copenhagen, Denmark, of 371 (280 male, 91 female) bladder cancer cases (including papillomas) and 771 controls. The participation rate, as given in a previous paper (Jensen *et al.*, 1983), was 94% among the cases and 75% among the controls. The RR for coffee users *versus* non-users, adjusted for age, sex, smoking (never/ever, plus a measure of pack years) was [approximately 1.4] in men and women combined, and the trend in risk with dose was not significant. The RRs were 1 (referent), 1.4, 1.2, 1.4 and 1.8 for subsequent levels of coffee use. The point estimates tended to be above unity for female coffee drinkers, but they were not dose-related.

Claude *et al.* (1986) conducted a case-control study of lower urinary tract cancer (90% were bladder tumours) in the Federal Republic of Germany. A total of 431 cases (340 male, 91 female) were matched for age and sex with 431 controls, who were primarily patients in hospitals for urological diseases (79%) and in homes for the elderly (21%). Only about 2% of cases refused to participate. The results were presented for each sex separately after allowance for smoking (never/ever and lifetime consumption in packs). In people of each sex, the RRs were above unity for coffee drinkers; the point estimates for more than four cups per day were 2.3 in males and 2.2 in females, and the trend in risk was significant for males. The RRs associated with coffee drinking were similar in smokers and nonsmokers. In this study, a positive association was found with total daily fluid intake, with a particularly high RR in males. The RR for drinking decaffeinated coffee *versus* that for non-users was 1.6 in males and 1.0 in females.

Piper *et al.* (1986) described a population-based case-control study of bladder cancer in women (aged 20-49) conducted in New York State in 1975-80. Information was available through telephone interviews on a total of 173 age-matched pairs, for a participation rate of 68% among cases and 71% among community controls. The crude RR for drinking brewed coffee was 1.6. The RR increased with dose, but the trend was not statistically significant.

In a study in Spain, based on 353 male and 53 female cases of bladder cancer compared with equal numbers of hospital controls without malignant or urological conditions (Bravo *et al.*, 1986, 1987), a positive association emerged among males for drinking 'espresso' coffee, with RRs of 1.9 for fewer than three cups and 2.6 for three or more cups per day. For women, the RR for daily use of coffee was [2.3], of borderline statistical significance. [The Working Group noted that details of the response rate were not given, and no allowance was made for any covariate, including smoking.]

Kabat *et al.* (1986) studied bladder cancer in nonsmokers among 76 male and 76 female cases and 238 male and 254 female hospital controls matched for sex, race, hospital and year of interview; the male controls consisted of 67% cancers not related to tobacco smoking and 33% non-neoplastic conditions; the female controls consisted of 59% and 41%, respectively. No association with brewed coffee was observed in either sex [overall RR adjusted for sex, 1.1; 95% CI, 0.8-1.5], and all subsequent risk estimates with dose were close to unity. Similarly, no association was evident with decaffeinated coffee use.

The RR for coffee drinking was significantly above unity (2.4; 95% CI, 1.4-4.4) in a study of 99 male cases of histologically confirmed bladder cancer and two groups each of 99 controls (one hospital, one neighbourhood) in La Plata, Argentina (Iscovich *et al.*, 1987). A positive trend in risk with dose was found, which persisted after allowance for smoking. The refusal rate was negligible (less than 3% of cases and 5% of controls). [The Working Group noted the limited size of the study and that an unstated number of re-interviews were undertaken to obtain missing information or to correct inconsistencies.]

In a population-based case-control study in Utah, USA, Slattery *et al.* (1988) obtained data on a total of 419 cases of bladder cancer and 889 controls (participation rate, 76% among cases and 82% among controls). A substantial proportion of the Utah population belongs to the Mormon church, which proscribes the use of coffee and tea, besides alcohol and tobacco. The RR for coffee consumption, adjusted for age, sex, diabetes, bladder infections and cigarette smoking was [approximately 1.2]. No consistent dose-response was evident, since the RR was 1.2 for up to 20 servings per week, 1.1 for 21-40 and 1.6 for over 40. Similarly, no association emerged in relation to drinking decaffeinated coffee (RR, 1.0).

In a study in Italy, Ciccone and Vineis (1988) studied coffee drinking among cases of bladder cancer (512 men, 55 women) from the main hospital of Turin; controls were 596 men and 202 women with urological or surgical conditions. The overall participation rate was 82% for cases (although there were only 2% refusals) and 98% for controls. With current coffee use, the overall RR, adjusted for smoking (never, ex- or current smoker) was [1.0] for men and [0.9] for women. There was no evidence of an increase in risk with increasing intake: in both men and women, the adjusted RR for four cups per day or more was 0.8. Similarly, no association was evident for either sex for past use (10 years before interview). The authors noted that the only subgroup with an elevated risk and a dose-response relationship was male nonsmokers.

Risch *et al.* (1988) analysed the association between drinking of coffee, tea and other beverages in a population-based case-control study on dietary factors and bladder cancer based on 826 cases of histologically confirmed bladder cancer and 792 controls in Canada. The participation rate was 67% for cases and 53% for controls. For total coffee consumption, the RR was 0.9 in males and 1.9 in females. Adjustment was made for history of diabetes and cigarette use in terms of cumulated pack-years. There was no association in either sex with frequency of use, and the RRs for the highest intake level (over six cups per day) were 0.9 for males and 1.1 for females. [The Working Group noted that the participation rates were lower than in other case-control studies.]

La Vecchia *et al.* (1989b) provided information on the coffee consumption of 163 patients with histologically confirmed bladder cancer (136 male, 27 female), from a network of hospitals in northern Italy, and of 181 controls with acute, nonneoplastic or urological conditions. The participation rate was over 98%. Compared with non- or moderate coffee drinkers, the RRs adjusted for age, sex, area of residence, social class and smoking were 2.0 for intermediate and 1.6 for heavy drinkers; the trend was not significant.

Renal pelvis and ureter. The etiology and pathogenesis of transitional-cell cancer of the renal pelvis and ureter are in several aspects similar to those of bladder cancer, although the frequency of cancer at these sites is much lower and, hence, the studies are based on small data sets.

One study in the USA (Schmauz & Cole, 1974), based on 43 cases of cancer of the renal pelvis and ureter and 451 population controls, showed a positive association with high levels of coffee consumption among men (RR for over seven cups per day, 14.9; 95% CI, 2.4-94.3).

Table 32. Summary of results of case–control studies of bladder cancer and coffee consumption: users *versus* nonusers[a]

Reference and location	Subjects (cases, controls)	Relative risk (95% CI)	Significance[b]	Comments
Cole (1971) USA	Men (345, 351)	1.2 (0.8–1.9)	NS	Adjusted for age and smoking (nonsmokers/ <½pack/≥½ pack per day). Similar relation among nonsmokers non-occupationally exposed to carcinogens
	Women (100, 100)	2.6 (1.3–5.1)	Significant	
Dunham *et al.* (1968); Fraumeni *et al.* (1971) USA	Men and women (493, 527)	1.5	NS; significant in black women	Adjusted for age and cigarette smoking
Morgan & Jain (1974) Canada	Men (158, 158)	[0.7]	NS	Unadjusted; mailed questionnaire
	Women (74, 74)	[1.3]	NS	
Simon *et al.* (1975) USA	Women (135, 390)	2.1 (1.1–4.3)	Significant	[RR, 1.9] (NS) after adjustment for smoking in two categories
Wynder & Goldsmith (1977) USA	Men (574, 574)	[1.5]	NS	Adjusted for smoking (four levels)
	Women (158, 158)	[1.3]	NS	
Miller *et al.* (1978) Canada	Men (183, 366)	1.3	NS	
	Women (72, 144)	1.6 [1.0–2.9]	NS	
Mettlin & Graham (1979) USA	Men and women (569, 1025)	[1.5 (0.9–2.5)]	NS	Adjusted for smoking (two levels) from published data
Howe *et al.* (1980) Canada	Men (480, 480)	1.4 (0.9–2.0)	NS	Unadjusted estimates from matched analysis
	Women (152, 152)	1.0 (0.5–2.1)	NS	
Cartwright *et al.* (1981) UK	Men (631, 789)	1.1 (0.9–1.4)	NS	Adjusted for age, type of case (incident/prevalent) and smoking; no heterogeneity according to type of coffee (instant/ground)
	Women (210, 271)	0.8 (0.6–1.2)	NS	

Table 32 (contd)

Reference and location	Subjects (cases, controls)	Relative risk (95% CI)	Significance[b]	Comments
Morrison *et al.* (1982) USA, UK and Japan	Men and women (1417, 1839)	1.0 (0.8–1.2)	NS	Adjusted for age, sex, study area and smoking
Najem *et al.* (1982) USA	Men and women (75, 142)	1.8 (0.1–10.0)	NS	Unadjusted estimates; low power
Sullivan (1982) USA	Men and women (82, 169)	Not given	Significant difference in average mean intake of ground coffee in white men, decaffeinated ground in white women	No relation with duration; unadjusted covariates
Hartge *et al.* (1983) USA	Men and women (2982, 5782)	1.4 (1.1–1.8)	Significant	Adjusted for sex, age, race, geographical area and tobacco history
Marrett *et al.* (1983)[c] USA	Men Women (412, 493)	1.3 [1.1–1.6] 1.1 [0.8–1.4]	Significant NS	Adjusted for age and smoking
Mommsen *et al.* (1983a,b) Denmark	Men (165, 165) Women (47, 94)	No association 2.6 (0.4–18.8)	 NS	Details not given for men; only one female case and five controls non-coffee drinkers
Rebelakos *et al.* (1985) Greece	Men and women (300, 300)	1.7 (1.2–2.3)	Significant	$\geq$2 *versus* < 2 cups per day; adjusted for age, sex and smoking
Gonzáles *et al.* (1985) Spain	Men and women (58, 116)	[0.6]	NS	'Habitual consumers'
Jensen *et al.* (1986) Denmark	Men and women (371, 771)	[~1.4]	NS	Including papillomas; adjusted for age, sex, smoking (never/current; lifetime pack years), tea and soft drinks
Claude *et al.* (1986) Federal Republic of Germany	Men (340, 340) Women (91, 91)	1.8 1.1	NS NS	Adjusted for smoking (never/ever; lifetime pack years). Significant trend in men

Table 32 (contd)

Reference and location	Subjects (cases, controls)	Relative risk (95% CI)	Significance[b]	Comments
Piper *et al.* (1986) USA	Women (173, 173)	1.6 (0.8–3.3)	NS	Aged 20–49; unadjusted
Bravo *et al.* (1986) Spain	Men (353, 353)	1.9 (1.4–2.6)	Significant	Matched for age and area of residence; unadjusted
	Women (53, 53)	[2.3 (1.1–5.1)]	Significant	
Kabat *et al.* (1986) USA	Men (76, 238) Women (76, 254)	[1.1 (0.8–1.5)]	NS	Nonsmokers only; adjusted for sex
Iscovich *et al.* (1987) Argentina	Men (99, 198)	2.4 (1.4–4.4)	Significant	Adjusted for smoking
Slattery *et al.* (1988) USA	Men and women (419, 889)	[~1.2]	NS	Adjusted for age, sex, diabetes, bladder infections and smoking
Ciccone & Vineis (1988) Italy	Men	[1.0]	NS	Adjusted for smoking (never, ex-, current)
	Women (567, 798)	[0.9]		
Risch *et al.* (1988) Canada	Men	0.9 (0.6–1.3)	NS	Adjusted for smoking (cumulated pack years) and history of diabetes
	Women (826, 792)	1.9 (1.0–3.4)	Significant	
La Vecchia *et al.* (1989b) Italy	Men and women (163, 181)	[1.8]	Significant	Adjusted for age, sex, area of residence, social class, smoking

[a] In square brackets, calculated by the Working Group

[b] NS, not significant

[c] Some overlap with the study of Hartge *et al.* (1983)

Table 33. Summary of results of case–control studies of bladder cancer and coffee consumption: dose–response relationships

Reference and location	Sex	Relative risk for level of coffee consumption[a]							Significance (trend; p)
		I Lowest	II	III	IV	V	VI	VII Highest	
Cole (1971)	Men	1	1.3	1.2	1.3	–	–	–	Not given
USA	Women	1	1.6	3.8	2.2	–	–	–	
Fraumeni *et al.* (1971)	Men, white	1	1.4	2.0	1.7	–	–	–	Not given
	Men, black	1	2.1	2.9	2.1	–	–	–	
USA	Women, white	1	0.7	0.5	0.3	–	–	–	
	Women, black	1	10.0	4.6	2.2	–	–	–	
Morgan & Jain (1974)[b]	Men and women	[1	0.6	0.9	0.8	1.1]	–	–	Nonsignificant
Canada									
Simon *et al.* (1975)[b]	Women	1	2.2	1.9	2.3	–	–	–	0.28
USA									
Wynder &	Men	1	1.4	1.9	2.0	–	–	–	Nonsignificant
Goldsmith (1977)	Women	1	1.0	1.9	1.3	–	–	–	Nonsignificant
USA									
Mettlin & Graham (1979)	Men and women	1	[1.2	1.1	1.8	1.3]	–	–	Nonsignificant
USA									
Howe *et al.* (1980)[b]	Men	1	[1.6	1.3	1.5]	–	–	–	Nonsignificant
Canada	Women	1	[0.7	1.7	1.3]	–	–	–	Nonsignificant
Morrison *et al.* (1982)									
USA	Men	1	0.8	0.7	0.9	0.8	0.8	1.5	Nonsignificant
	Women	1	0.8	0.6	1.7	0.9	0.7	1.0	Nonsignificant
UK	Men	1	1.1	0.9	0.9	0.8	–	–	Nonsignificant
	Women	1	1.4	0.4	1.2	1.0	–	–	Nonsignificant
Japan	Men	1	1.0	1.2	1.3	1.9	–	–	Nonsignificant
	Women	1	0.7	–	0.7	–	–	–	Nonsignificant
Hartge *et al.* (1983)	Men	1	0.9	1.0	1.1	1.0	1.2	1.5	Nonsignificant
USA	Women	1	0.9	0.8	0.9	0.7	0.9	0.8	Nonsignificant
Marrett *et al.* (1983)[c]	Men	1	1.6	2.0	2.0	–	–	–	Significant
USA	Women	1	[1.3	1.2	1.0]	–	–	–	Nonsignificant

Table 33 (contd)

Reference and location	Sex	Relative risk for level of coffee consumption[a]							Significance (trend; p)
		I Lowest	II	III	IV	V	VI	VII Highest	
Rebelakos *et al.* (1985) Greece	Men and women	1	1.2	1.7	2.7	0.7	–	–	0.02
Jensen *et al.* (1986) Denmark	Men and women	1	1.4	1.2	1.4	1.8	–	–	0.12
Claude *et al.* (1986)	Men	1	1.4	1.4	2.3	–	–	–	< 0.05
Federal Republic of Germany	Women	1	1.3	1.9	2.2	–	–	–	Nonsignificant
Piper *et al.* (1986)[d] USA	Women	1	0.9	1.9	2.1	–	–	–	Nonsignificant
Bravo *et al.* (1986, 1987)[b] Spain	Men	1	1.9	2.6	–	–	–	–	< 0.01
Kabat *et al.* (1986)[b]	Men	1	0.9	1.4	1.4	0.5	–	–	Nonsignificant
USA	Women	1	1.5	0.8	0.7	2.4	–	–	Nonsignificant
Iscovich *et al.* (1987) Argentina	Men and women	1	1.1	4.5	12.0	–	–	–	< 0.01
Slattery *et al.* (1988) USA	Men and women	1	1.2	1.1	1.6	–	–	–	Nonsignificant
Ciccone & Vineis (1988)	Men	1	0.8	1.0	1.2	0.8	–	–	Nonsignificant
	Women	1	1.4	1.0	0.7	0.8	–	–	Nonsignificant
Italy									
Risch *et al.* (1988)	Men	1	1.0	1.2	0.9	–	–	–	Nonsignificant
Canada	Women	1	1.0	1.9	1.1	–	–	–	Nonsignificant
La Vecchia *et al.* (1989b) Italy	Men and women	1	2.0	1.6	–	–	–	–	Nonsignificant

[a] The levels relate to different quantities in each study; therefore, they offer information for analyses within each study but not for comparisons between studies. 1, lowest (referent) level; 7, highest level

[b] Crude risks

[c] Some overlap with the study of Hartge *et al.* (1983)

[d] Adjusted risks, but not stated whether smoking included

A matched hospital-based study of 33 cases of cancer of the renal pelvis and 33 controls in the UK (Amstrong *et al.*, 1976) found no positive association with coffee [RR, 0.2; $p < 0.01$]. Indeed, there was a significant excess of cases who had never consumed coffee regularly.

A population-based case-control study of 74 cases and 697 controls in the USA (McLaughlin *et al.*, 1983) showed no consistent association between cancer of the renal pelvis and coffee drinking in people of either sex after adjustment for smoking (RR, 1.6 for men, 0.5 for women).

The largest study on cancer at this site (187 case-control pairs) was conducted in Los Angeles County, USA, using telephone interviews for cases and neighbourhood controls (Ross *et al.*, 1989). Heavy coffee drinkers had an apparently elevated risk for cancer of the renal pelvis and ureter (RR for seven cups or more per day, adjusted for cigarette smoking, 1.8), but the trend in risk with dose was not significant.

Kidney: The causes of renal-cell cancer (adenocarcinoma of the kidney) are less well defined but are certainly, at least in part, different from those of cancer of the urinary tract.

In a case-control study conducted in several areas of the USA between 1965 and 1973 on 202 patients with adenocarcinoma of the kidney and 394 hospital controls, Wynder *et al.* (1974) found no significant difference in daily coffee consumption within each smoking category: [RR, 0.6, 0.9 and 1.1 for 1-2, 3-4 and $\geq$5 cups per day).

Armstrong *et al.* (1976) conducted a case-control study of 106 cases of adenocarcinoma of the renal parenchyma and 106 controls in Oxford, UK, and found neither an association with coffee use [RR, 1.1] nor a dose-response relationship.

McLaughlin *et al.* (1984) conducted a population-based case-control study on 495 cases of renal-cell carcinoma and 697 controls from the Minneapolis-St Paul seven-county metropolitan area (USA). The RR for ever having drunk coffee was 1.0 (95% CI, 0.6-1.8) in men and 1.4 (0.7-2.9) in women. In neither was a dose-response relationship observed.

Goodman *et al.* (1986) conducted a hospital-based case-control study of renal-cell carcinoma among 189 men and 78 women from various areas of the USA. For coffee drinking, the RRs (for the two sexes combined) were 0.7 for one to two cups per day and 0.8 for three or more compared with non-coffee drinkers. The RR for ever having drunk decaffeinated coffee was 1.9 (95% CI, 1.0-3.6), but people drinking one to two cups per day had a RR of 2.0 while those drinking three cups or more had a RR of 1.3.

In a study of 166 incident cases of renal-cell carcinoma and an equal number of age-, sex- and race-matched neighbourhood controls, Yu *et al.* (1986) found an association in women for daily coffee consumption (RR, 2.3; $p = 0.06$) in the absence of a direct dose-response relationship. No significant association was observed in men.

A study from Australia (McCredie *et al.*, 1988) based on 360 cases of cancer of the renal parenchyma and 985 population controls found no association with coffee consumption, but no precise information is given in the text.

(ii) *Pancreas*

Twenty-one case-control studies have reported on the relationship between coffee consumption and pancreatic cancer; these data are summarized in Table 34 on p. 140.

As part of a study of cancer at 13 sites, Lin and Kessler (1981) reported on 109 histologically confirmed cases (67 male, 42 female) of pancreatic cancer (94 adenocarcinomas and 15 islet-cell tumours) identified in 1972-75 in more than 115 hospitals in the USA. Equal numbers of hospital controls were matched for age, sex, race, hospital and year of admission. Most of the cases and controls were interviewed while in hospital by a person who was unaware of the diagnosis of the patient. Overall 86% of eligible subjects were interviewed. It was reported in a letter that an association was found with drinking decaffeinated coffee but not with total coffee consumption: 91% of the cases drank coffee compared to 93% of controls, but 41% of cases drank decaffeinated coffee compared to only 25% of controls ($p < 0.01$) (Kessler, 1981).

MacMahon *et al.* (1981a,b; the latter study was reported in a letter) reported on 367 histologically confirmed cases (216 male, 151 female) of pancreatic cancer (excluding islet-cell tumours) out of 578 patients under 80 years of age identified in 11 hospitals in Boston and Rhode Island, USA. There were 643 hospital controls, out of 1118 eligible patients, who had been at hospital at the same time as the cases; 254 had diseases other than cancer at sites other than the gastrointestinal tract, 157 had cancers other than in the gastrointestinal tract, 117 had diseases of the gastrointestinal tract other than cancer, and 115 had gastrointestinal cancer. Each case and control pair was interviewed personally by the same physician. The main reasons for failure to participate were death (20 cases, 9 controls), early discharge (35, 131), illness (78, 179), language difficulties (14, 26) and refusal (26, 73). An increased risk was found for both men and women. The RR of coffee drinkers *versus* non-coffee drinkers was 2.6 for men and 2.3 for women. No dose-response was observed in men, but a significant trend with consumption was found in women, rising to a risk of 3.1 for women who drank five or more cups per day. These risks persisted after adjustment for cigarette smoking.

Several generally smaller studies (Elinder *et al.*, 1981; Jick & Dinan, 1981; Goldstein, 1982; Severson *et al.*, 1982) reported essentially negative results. The study of Jick and Dinan (1981), published as a letter, which gave few details, was based on 83 cases and 161 hospital controls aged < 80 years in several countries matched 2:1 for age, sex, hospital and year of admission and used a standard personal hospital interview. Elinder *et al.* (1981) conducted two studies: In one, they used information from certificates of deaths in 1961-74 in two small Swedish parishes; the study was based on 21 male cases and 51 deceased male controls obtained from a random sample of deaths in the same parish and matched for age. Next-of-kin, usually wives, were interviewed. The second study was based on 41 twin pairs, born 1886-1925, both of whom were alive in 1961 and one of whom developed pancreatic cancer. Information was obtained from postal questionnaires. The study of Goldstein (1982) was based on 91 histologically verified cases of pancreatic cancer diagnosed in 1973-80 in San Diego, CA, USA; controls were patients with cancer of the prostate (45) and breast (48). Routine hospital interview data were used. Severson *et al.* (1982) based their study on 22 cases aged 40-79 from a registry that was part of the SEER (Surveillance, Epidemiology and End Results) Program in Seattle, WA, USA, 1977-80, and on a random population sample of controls. Next-of-kin were interviewed for most of the cases (20), whereas personal interviews were obtained for controls. The last two studies were also published as letters, which contained few details.

A large study of 275 histologically verified cases (153 men, 122 women) aged 20-80 interviewed in 1977-81 and of 7994 hospital controls also gave negative results, with risk ratios very near to unity after adjustment for smoking (Wynder *et al.*, 1983). This was part of a large study of tobacco-related cancers in six US cities; controls were patients with non-tobacco-related diseases: 42% had other cancers, 10% had benign neoplasms and 7% had trauma. Personal interviews were carried out within six months of diagnosis. During the last year of interviewing, 45% of potential cases and 35% of potential controls completed interviews. The main reasons for not interviewing cases were death, early discharge, illness and personal or physician refusal. The main reason for not interviewing controls was that their initial diagnosis had been made more than six months before interview.

Kinlen and McPherson (1984) re-evaluated data from the case-control study of Stocks (partly reported by Stocks, 1957) on data collected in north-west England and north Wales in 1952-54 on 216 cases (109 men, 107 women) aged > 40 years. These were compared with 432 controls, who were patients with other cancers in the original study, matched 2:1 for age, sex and area of residence; cancers of the lung, bladder, mouth, pharynx, oesophagus, gastrointestinal tract and ovary were excluded, and controls were thus patients with breast cancer (38%), prostatic cancer (19%), leukaemia or lymphoma (19%), renal cancer (7%) and other cancers

(17%). No relation with coffee consumption was found either before or after adjustment for smoking.

Subsequent studies by Gold *et al.* (1985), Mack *et al.* (1986) and Norell *et al.* (1986) all provided some evidence of an association. In the study of Gold *et al.* (1985), 201 cases (94 men, 107 women) were interviewed and included in a matched analysis out of a total of 392 patients with pancreatic cancer from 16 hospitals in Baltimore, MD, USA, in 1977-80. Seventy-two patients refused to be interviewed, physician consent was not obtained for 36, and 10 patients could not be traced or had died and no relative could be found. Of the 201, 25% had a personal interview; for 35% the spouse was interviewed and for 40%, another relative. Two control groups were used: a matched hospital series (for age, race, sex, hospital, date of admission) in which patients with other cancers were excluded (30% had heart or other circulatory disease and 13% had digestive disease) and a population-based group that was chosen by random-digit dialling, matched by age, race, sex and telephone exchange and interviewed by telephone. Participation was about 50% of 'eligible' individuals in both control series; a total of 20 706 telephone numbers and 37 033 calls were made to find eligible controls. A nonsignificant relationship was found among women only, but this was less apparent when smoking was adjusted for.

Mack *et al.* (1986) conducted a study of 490 histologically confirmed cases (282 male, 208 female) of adenocarcinoma of the exocrine pancreas in patients aged <65 years, comprising all those registered in Los Angeles county, and an equal number of neighbourhood controls matched for age, sex, race and neighbourhood in Los Angeles, CA, USA. Home interviews were conducted; for cases, about 25% of the interviews were with the case, 53% with the spouse and 19% with a first-degree relative. Cases were selected from 736 eligible cases; losses were due to failure to locate the case (77), physician refusal (43), patient refusal (86), language problems (10) and failure to find a matched control (17). Final medical review eliminated another 13 cases. Results for coffee drinking showed a significant relationship, which persisted after adjustment for smoking.

Norell *et al.* (1986) conducted a study in Stockholm and Uppsala, Sweden, in 1982-84, based on 99 cases (55 male, 44 female) aged 40-79 out of 120 that were eligible, 138 population controls (a sample from the same parish matched for age and sex) out of 162 that were eligible and 163 hospital controls who were a random sample of patients with inguinal hernia, of whom 179 were eligible. Of the cases, 61% were verified by resection or autopsy, 33% by radiology and biopsy, and 6% by clinical examination and radiology. Cases and hospital controls were given a questionnaire at the time of diagnosis, whereas population controls were sent a postal questionnaire followed by a telephone call when necessary. The results were positive when hospital controls were used and disappeared when population

controls were the basis of comparison. Results adjusted for smoking were not presented.

Wynder *et al.* (1986) undertook a study of 238 patients (127 men, 111 women) and 696 controls in 18 hospitals in six US cities, 1981-84, in which both coffee and decaffeinated coffee were examined. Controls were selected from among patients with non-tobacco-related diseases matched for age, sex, race, hospital and year of interview; 62% had other cancers. A hospital interview was used. Neither exposure was related to pancreatic cancer either before or after adjustment for smoking.

A study (reported in a letter to the Editor of *The New England Journal of Medicine*) of 172 patients (85 men, 87 women) aged < 80 years with histologically verified pancreatic cancer and 267 controls was conducted in 1981-84 in Boston and Rhode Island, MA, USA, on the basis of hospital interviews (Hsieh *et al.*, 1986). Controls had the same physician, and the main diagnoses were cancer of the breast, colon, stomach or uterus, benign tumours, hernia, colitis, enteritis and bowel obstruction. An elevated risk, of borderline significance, was found only in patients who had drunk more than five cups of coffee per day, the RR being 2.4 in men and 2.2 in women. Similar results were found for coffee and for decaffeinated coffee.

A study was carried out in northern Italy of 150 histologically verified cases aged < 75 (99 men, 51 women) and 605 hospital controls with acute conditions except cancer, digestive-tract disorders or conditions related to coffee, alcohol or tobacco consumption (33% trauma, 12% other orthopaedic, 42% general surgery) (La Vecchia *et al.*, 1987). More than 98% of eligible patients (cases and controls) agreed to participate and were given a hospital interview. Some evidence of risk was seen, but there was no dose-response relationship and the highest risk was found among people who drank one to two cups per day. Only 16 cases did not drink coffee. No relationship with decaffeinated coffee was found.

Studies by Raymond *et al.* (1987), based on 88 cases (43 male, 45 female), 67% of which were verified histologically, and 336 population controls, and by Falk *et al.* (1988), based on 363 cases (203 male, 160 female) out of 427 incident cases and 1234 hospital controls, gave negative results. In the first study, personal interviews were obtained from cases identified through the Geneva, Switzerland, registry in 1976-81 and from controls who were contacted by letter. The study by Falk *et al.* (1988) was carried out in Louisiana, USA; 82% of cases were confirmed histologically and the remainder by X-ray, ultrasound or clinical examination. Controls were matched for hospital, age, sex and race and excluded patients with cancer, diabetes, circulatory disorders and digestive or respiratory diseases. Direct interviews were carried out with 50% of cases, and 50% were with next of kin.

A small study by Gorham *et al.* (1988) of 30 cases (out of 51 eligible) and 47 controls (out of 58 eligible) was based only on death certificates in Imperial County, CA, USA, in 1978-84. Controls were matched for age, sex, race and year of death;

cancer patients were excluded, and 47% had died from heart disease, 17% from cerebrovascular disease, 4% from pneumonia and 4% from chronic obstructive pulmonary disease. The estimated RR for three or more cups of coffee a day was [2.7] compared to less than three cups, which dropped to [1.9] and was nonsignificant after adjustment for smoking. [The Working Group noted that only 30 of 51 deaths from pancreatic cancer were included; hospital records were not examined.]

Clavel *et al.* (1989) conducted a hospital interview study in Paris, France, with 161 cases (98 male, 63 female), 63% of which were histologically verified (28% by surgery and 9% by clinical examination) in 1982-85. There were 268 hospital controls: 129 had other cancers, excluding biliary, liver, stomach, oesophagus, respiratory and bladder cancers, and 139 had non-neoplastic disease. All were matched to cases for age, sex and hospital interviewer. None of the cases and about 5% of controls refused to participate. After adjustment for education, alcohol and smoking, a nonsignificant trend was found for males, giving a RR of 2.1 for four or more cups/day. In females, a significant trend was observed, and the observed risk for more than four cups per day was 9.6. Unusually high risks were seen in women and in persons who had never drunk alcohol.

A study of 216 cases (123 male, 93 female) and 279 controls was carried out in the UK for 1983-86 (Cuzick & Babiker, 1989), based on personal interview. Of the cases, 30% were verified histologically, 23% by surgery and 47% by clinical examination or imaging. The controls included 212 hospital controls without other cancers or other chronic medical conditions: 27% had fractures, 23%, hernia, 15%, varicose veins and haemorrhoids and 11%, genitourinary diseases; the remaining 67 were population controls. The study gave essentially negative results, although a slightly elevated risk was seen in cases whose current consumption was more than five cups per day (RR, 1.4). This trend disappeared when consumption approximately 10 years previously was examined.

A case-control study in the USA involved 212 cases (140 of which were confirmed pathologically) identified from death certificates, out of 262 that were eligible, and 250 population-based controls contacted by random telephone dialling and matched to cases by age within five years (Olsen *et al.*, 1989). Family members (usually widow or spouse) were interviewed on the case's use of cigarettes, alcohol, coffee and other dietary factors two years prior to death of the patient or prior to interview. Coffee was not a risk factor (odds ratio for seven cups or more per day, 0.6; 95% CI, 0.3-1.3).

Table 34. Summary of results of case-control studies of coffee drinking and pancreatic cancer

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Lin & Kessler (1981); Kessler (1981) USA	Men and women (109, 109)			91% cases *vs* 93% controls drank coffee 41% cases *vs* 25% controls drank decaffeinated coffee ($p < 0.01$)
MacMahon *et al.* (1981a,b) USA	Men (216, 307)	0 1–2 3–4 ≥5	1.0 2.6 2.3 2.6	χ^2 trend = 1.5
	Women (151, 336)	0 1–2 3–4 ≥5	1.0 1.6 3.3 3.1	χ^2 trend = 13.7
	Men and women	0 1–2 ≥3	1.0 1.8 2.7	Adjusted for smoking; χ^2 trend = 10.6
Jick & Dinan (1981) Several countries	Men and women (83, 166)	0 1–5 ≥6	1.0 0.7 0.5	
Elinder *et al.* (1981) Sweden	Men (21, 51) Cases Controls	 5.3 ± 2.1 (SD) 6.1 ± 2.4		95% CI for difference: –2.9–0.2
	Men and women (twins; 41, 41)	3.8 3.6		95% CI for difference –0.33–0.77
Goldstein (1982) USA	Men and women (91, 93)	0 1–2 3–4 ≥5	1.0 1.8 1.0 1.6	Crude odds ratio; χ^2 for trend nonsignificant
Severson *et al.* (1982) USA	Men and women (22, 485)	Current	1.0 (0.2–4.5)	Adjusted for age, sex, smoking
Wynder *et al.* (1983) USA	Men (153, 5469)	0 1–2 3–4 ≥5	1.0 [1.1] 1.0 1.4	

Table 34 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Wynder *et al.* (1983) (contd)	Women (122, 2525)	0 1–2 3–4 ≥5	1.0 [1.0] 1.0 1.2	
	Men	0 1–2 3–4 ≥5	1.0 [1.0] 1.0 1.0	Adjusted for smoking
	Women	0 1–2 3–4 ≥5	1.0 0.9 0.9 1.0	Adjusted for smoking
Kinlen & McPherson (1984) UK	Men (109, 218)	Never Weekly Daily	1.0 0.9 0.9	
	Women (107, 214)	Never Weekly Daily	1.0 1.3 0.9	Adjusted for tea and smoking
Gold *et al.* (1985) USA	Men (94, 96/96)	0 1–2 3–4 ≥5	1.0 1.6/1.5 1.5/1.0 1.0/1.3	Adjusted for age; hospital random-digit dialling controls; χ^2 for trend, [0.02/0.4]
	Women (103, 103/104)	0 1–2 3–4 ≥5	1.0 0.8/1.2 2.0/1.6 2.1/2.9	χ^2 for trend, [3.8/2.7]
Mack *et al.* (1986) USA	Men and women (490, 490)	0 1–4 ≥5	1.0 1.6 2.0	Crude odds ratio
	Men and women	0 1–4 ≥5	1.0 [1.4] [1.6]	Adjusted for smoking
Norell *et al.* (1986) Sweden	Men and women (99, 163/138)	0–1 2–4 ≥5	1.0 1.7/1.6 (0.7–3.9/0.8–3.2) 1.9/1.0 (0.8–4.9/0.4–2.6)	Hospital/population controls; 90% CI

Table 34 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Wynder *et al.* (1986) USA	Men (127, 371)	0	1.0	
		1–2	[1.1]	
		≥3	[1.5]	
	Women (111, 325)	0	1.0	
		1–2	[0.7]	
		≥3	[1.0]	
	Men	0	1.0	Decaffeinated
		1–2	0.8	
		≥3	0.7	
	Women	0	1.0	
		1–2	1.6	
		≥3	0.9	
Hsieh *et al.* (1986) USA	Men (85, 129)	0	1.0	Consumption ~10 years previously; χ^2 for trend, [2.8]
		1–2	1.1	
		3–4	1.0	
		≥5	2.4	
	Women (87, 138)	0	1.0	χ^2 for trend, [1.3]
		1–2	1.3	
		3–4	1.0	
		≥5	2.2	
	Men and women (170, 265)	0	1.0	Total consumption of coffee; χ^2 for trend, [3.3]
		< 20.000	1.0	
		20–39 000	1.3	
		40–59 000	1.8	
		≥60 000	1.4	
	Men and women (170, 265)	0	1.0	Total consumption of decaffeinated coffee; χ^2 for trend, [2.1]
		< 20.000	1.0	
		20–39 000	1.0	
		40–59 000	1.5	
		≥60 000	1.6	
	Men and women (170, 266)	0	1.0	Total consumption of both types of coffee; χ^2 for trend, [2.4]
		< 20.000	1.4	
		20–39 000	1.2	
		40–59 000	2.0	
		≥60 000	1.5	
La Vecchia *et al.* (1987) Italy	Men and women (150, 605)	0	1.0	
		1–2	1.8	
		3–4	1.5	
		≥5	1.4	

Table 34 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
La Vecchia *et al.* (1987) (contd)	Men and women	0	1.0	Adjusted for smoking, alcohol, occupation
		1–2	1.7	
		3–4	1.4	
		≥5	1.1	
	Men and women	0	1.0	Decaffeinated coffee
		3–4	0.8	
	Men and women	0	1.0	Decaffeinated coffee; adjusted for smoking, alcohol, occupation
		3–4	0.9	
Raymond *et al.* (1987) Switzerland	Men and women (88, 336)	0	1.0	90% CI
		< 1.4 l/week	0.9 (0.5–1.8)	
		≥1.4 l/week	1.3 (0.7–2.3)	
	Men and women	0	1.0	Instant coffee; 90% CI
		Any	1.4 (0.8–2.4)	
Falk *et al.* (1988) USA	Men (203, 890)	0	1.0	Adjusted for smoking, alcohol, fruit consumption, income
		1–2	0.7	
		3–4	0.5	
		5–7	0.7	
		≥8	1.4	
	Women (160, 344)	0	1.0	Adjusted as above
		1–2	0.7	
		3–4	0.7	
		5–7	1.0	
		≥8	0.9	
Gorham *et al.* (1988) USA	Men and women (30, 47)	0	1.0	
		1–2	[0.5]	
		3–4	[1.2]	
		≥5	[2.3]	
Clavel *et al.* (1989) France	Men (98, 161)	0	1.0	χ^2 for trend, [1.2]
		1	1.1	
		2–3	1.5	
		≥4	2.1	
	Women (63, 107)	0	1.0	χ^2 for trend, [6.4]
		1	3.9	
		2–3	6.7	
		≥4	9.6	

Table 34 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Cuzick & Babiker (1989) UK	Men and women (216, 279)	0 1–2 3–4 ≥5	1.0 0.9 0.6 1.4	Adjusted for smoking; χ^2 for trend, 0.23
	Men and women	0 1–2 3–4 ≥5	1.0 0.9 0.6 1.4	Coffee consumption ~10 years previously; χ^2 for trend, 0.43
Olsen *et al.* (1989) USA	Men and women (212, 220)	<1 1–3 4–6 ≥7	1.0 0.5 0.7 0.6	Odds ratio, adjusted for smoking, diet

(iii) *Breast cancer*

Case-control studies of breast cancer and coffee, instant coffee and decaffeinated coffee are summarized in Table 35 (p. 147).

Lawson *et al.* (1981) analysed data obtained from the Boston Collaborative Drug Surveillance Program and from a collaborative study conducted in the USA, Scotland and New Zealand. Cases were 241 women discharged with a diagnosis of breast cancer. Three controls were matched to each case for age, smoking habit, study and country. Coffee and tea drinking were grouped as 'hot beverage consumption'. Compared to those who did not drink coffee or tea, RRs for those who drank one to three, four to six and seven or more cups per day were 1.3, 1.5 and 1.1 (90% CI, 0.6-1.8 for the last category), respectively.

Lubin *et al.* (1981) reported the results of a study conducted in northern Alberta, Canada, during 1976-77. Interview was completed for 577 cases and 826 population controls. The response rate was 95% for cases and 72% for controls. Information on consumption of tea or coffee was obtained along with demographic, reproductive and medical histories and data on several food items. Tea and coffee consumption was analysed together: the age-adjusted RR when comparing more than five cups per day to five or fewer was 1.2 (95% CI, 0.9-1.5).

Mansel *et al.* (1982) in an abstract reported the results from an analysis of a computer data base of 20 000 hospital in-patients with a diagnosis of breast disease. These patients were compared with a matched non-breast disease group. As compared with non-coffee drinkers, coffee drinkers had an increased risk for breast cancer (RR, 1.3; 95% CI, 0.99-1.6). [It was not clear who was included in the control

group, what variables were matched on, whether matched analyses were carried out, and thus, what confounders had been controlled. Although information was collected on several doses levels, information on any dose-effect relation was not available.]

Lubin *et al.* (1984, 1985) conducted a hospital-based case-control study in Israel. Cases were histologically confirmed breast cancer cases in the greater Tel Aviv metropolitan area diagnosed between 1975 and 1979. Two control series, surgical and neighbourhood, were used; each was matched individually to a case by age (± five years), country of origin and length of residence in Israel. Neighbourhood controls were drawn from the national voting list and lived in the same voting district as the cases. Information was sought on the frequency of consumption of 250 food and beverage items as well as on selected hormonal, medical and demographic characteristics. Response rates among the eligible subjects were 96% for cases and surgical controls and 72% for neighbourhood controls. A total of 818 cases, 743 surgical controls and 813 neighbourhood controls were included in the analysis. Breast cancer cases were found to consume less coffee than both control series.

Rosenberg *et al.* (1984, 1985) analysed data obtained in a case-control programme for the surveillance of drug effects. Cases were 2651 in-patients in hospitals located in eastern USA who were interviewed between 1975 and 1982. There were two control groups: one consisted of 1501 women admitted for acute nonmalignant conditions (trauma or infections); the other comprised 385 women with malignancies (malignant melanoma, lymphoma and leukaemia). With either control group, RRs were close to 1.0 and there was no trend of increasing risk with increasing daily intake of coffee. Coffee drinking was not associated with breast cancer risk among subgroups of women stratified by age and reproductive history, history of fibrocystic breast disease, family history of breast cancer, or body mass index. Among a subset of subjects who did not drink caffeine-containing coffee, age-adjusted RRs were close to 1.0.

In a study in France, described by Lê *et al.* (1984) and reported in a letter by Lê (1985), 500 cases and 945 surgical controls with nonmalignant disease were studied. The risk for breast cancer was found to be inversely associated with reported current daily coffee consumption. Results were similar for women with and without a history of benign breast disease.

La Vecchia *et al.* (1986) conducted a hospital-based case-control study of breast cancer in Italy, beginning in 1980. There were 616 pairs of cases and controls. Adjusted RRs for coffee drinking were 1.0 for none, 1.6 (95% CI, 1.1-2.4) for less than two, 1.4 (1.0-2.0) for two to three and 1.1 (0.7-1.7) for four or more cups per day. There was no tendency for the risk of breast cancer to increase with increasing quantity or duration of coffee drinking.

Katsouyanni *et al.* (1986) conducted a hospital-based case-control study in Greece over a 12-month period in 1983-84. The study included 120 cases from two teaching hospitals in the Greater Athens area and 120 controls admitted for accidents and orthopaedic disorders in a third teaching hospital. Subjects were asked to indicate average frequency of consumption of 120 food or beverage items in the period preceding the onset of disease, along with information on demographic, socioeconomic, reproductive and medical variables. A test for a linear trend was not significant for coffee consumption.

Schairer *et al.* (1987) conducted a case-control study on participants in the Breast Cancer Detection Demonstration Project in the USA, a five-year screening programme begun in 1973. Cases were diagnosed from June 1977 to November 1980. Control subjects were women who had not been recommended for, and had not undergone, surgical evaluation during screening participation and were similar to breast cancer cases with regard to screening centre, age, ethnic origin, time of entry into the screening programme and length of participation in the programme. The number of daily servings of brewed, instant or decaffeinated coffee was not associated with increased risk for breast cancer.

Pozner *et al.* (1986) examined caffeine and coffee intake in women with breast cancer to determine whether it influences cell differentiation in tumours. Dietary history was obtained by interview with 106 women who had undergone mastectomy and axillary dissection for breast cancer at the Mount Sinai Medical Center in New York, USA. Information on tumour differentiation was missing for five women, leaving 101 with complete data. Tumours categorized as well or moderately differentiated were grouped (70 subjects) and compared to poorly differentiated tumours (31 subjects). Women with moderately to well differentiated tumours had had a higher intake of coffee (2.65 ± 2.23 cups per day) than women with poorly differentiated tumours (1.71 ± 1.43); the same trend was seen for caffeine and for all coffee, decaffeinated coffee, cola and tea. Stepwise logistic regression, with tumour differentiation as the dependent variable and coffee, both caffeinated and decaffeinated, tea, cola, cocoa, caffeine (mg/day), caffeine (mg per kg body weight per day), vitamin A, age and Quetelet's index as candidate independent variables, indicated that high coffee consumption is associated with moderately and well differentiated tumours; after accounting for differences in coffee intake, no other variable in the model emerged as significant. When logistic regression was performed including smoking, oral-contraceptive use, parity, number of children, age at first pregnancy, age at menarche, total calories, protein, total fat and other nutrients, however, no variable appeared to be significantly associated with degree of tumour differentiation. [The Working Group noted that this study is difficult to group with other studies of etiology. Also, factors that historically have been linked to breast cancer did not appear to influence tumour differentiation in this study.]

Mabuchi *et al.* (1985a) studied risk factors for male breast cancer as part of a larger case-control investigation of various rare cancers conducted over 1972-75 in a large number of hospitals in five US metropolitan areas. Cases were identified through continuous monitoring of documents in the hospital pathology and medical records departments. Controls were hospital patients free of cancer and matched to the cases for age (± three years), sex, race and marital status. Of the 64 eligible male breast cancer patients identified, 52 were interviewed, along with an equal number of controls. Matched analysis showed no difference in coffee or decaffeinated coffee consumption.

Table 35. Summary of results of case–control studies of breast cancer and coffee consumption

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% confidence interval)	Comments
Lawson *et al.* (1981) USA, Scotland, New Zealand	Women (241, 723)	0 1–3 4–6 ≥7	1.0 1.3 1.5 1.1 (0.6–1.8)	Coffee and tea; 90% CI
Lubin *et al.* (1981) Canada	Women (577, 826)	≤5 >5	1.0 1.2 (0.9–1.5)	Coffee and tea
Lubin *et al.* (1984, 1985) Israel	Women (738, 738) surgical controls	0 1 2–3 ≥4	1.0 0.7 (0.4–1.1) 0.7 (0.4–1.0) 0.7 (0.4–1.1)	Matched by age, country of origin, length of residence in Israel. Cases in the two comparisons involved the same series of subjects.
	(807, 807) neighbourhood controls	0 1 2–3 ≥4	1.0 0.5 (0.3–0.9) 0.5 (0.2–0.9) 0.6 (0.2–0.9)	
Rosenberg *et al.* (1984, 1985) USA	Women (2651, 1501) controls with non-malignant conditions	0 1–2 3–4 ≥5	1.0 1.2 (1.0–1.5) 1.2 (1.0–1.6) 1.2 (0.9–1.6)	Extensive adjustment made for known or suspected breast cancer risk factors
	(2651, 385) controls with cancers at other sites	0 1–2 3–4 ≥5	1.0 1.0 (0.7–1.4) 0.9 (0.7–1.3) 1.1 (0.7–1.6)	

Table 35 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% confidence interval)	Comments
Rosenberg *et al.* (1984, 1985) (contd)	(916, 584) controls with non-malignant conditions	0 1–2 3–4 ≥5	1.0 1.2 (0.9–1.5) 1.4 (0.9–1.8) 0.6 (0.3–1.1)	Decaffeinated coffee; adjusted for age
	(916, 138) controls with cancers at other sites	0 1–2 3–4 ≥5	1.0 1.1 (0.7–1.7) 1.1 (0.6–2.0) 1.0 (0.4–2.8)	Decaffeinated coffee; adjusted for age
Lê (1985) France	Women (500, 945)	Never 1–2 ≥3	1.0 0.8 0.6	Test for trend, p = 0.003; adjusted for known risk factors
La Vecchia *et al.* (1986) Italy	Women (616, 616)	0 <2 2–3 ≥4	1.0 1.6 (1.1–2.4) 1.4 (1.0–2.0) 1.1 (0.7–1.7)	Adjusted for known risk factors
Katsouyanni *et al.* (1986) Greece	Women (120, 120)	Frequency of use Tertile 1 2 3		Adjusted for age, interviewer, and length of schooling; nonsignificant inverse trend
Schairer *et al.* (1987) USA	Women (1510, 1882)	0 <1 2 3 4 ≥5	1.0 1.0 (0.8–1.3) 1.0 (0.7–1.2) 0.9 (0.7–1.2) 0.9 (0.7–1.3) 1.0 (0.8–1.3)	Crude, unmatched analysis; adjustment for other risk factors and types of caffeine-containing beverage did not change the results.
		0 <1 2 3 4 ≥5	1.0 0.9 (0.8–1.1) 0.9 (0.7–1.2) 0.9 (0.6–1.3) 0.9 (0.5–1.7) 0.7 (0.3–1.3)	Instant coffee

Table 35 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% confidence interval)	Comments
Schairer *et al.* (1987) (contd)		0	1.0	Decaffeinated coffee
		<1	1.0 (0.9–1.2)	
		2	1.0 (0.8–1.4)	
		3	0.7 (0.4–1.1)	
		4	0.9 (0.5–1.7)	
		≥5	1.1 (0.6–2.2)	
Mabuchi *et al.* (1985a) USA	Men (52, 52)	<1	(81% *versus* 83%, NS)	Matched on age, sex, race, marital status
		≥1		
		<1	(38% *versus* 31%, NS)	Decaffeinated coffee
		≥1		

(iv) *Ovary*

Case-control studies of ovarian cancer and coffee or decaffeinated coffee are summarized in Table 36 (p. 153).

Trichopoulos *et al.* (1981) reported data from a relatively small case-control study in Athens, Greece, showing a suggestive positive association between coffee consumption and risk of ovarian cancer of common epithelial types. The association was significant (two-tailed $p \sim 0.03$) when dose trends (cups of coffee per day, lifetime consumption of cups of coffee) were taken into account. [The Working Group noted that this study is not considered separately, since the relevant data are part of a larger subsequent study (Trichopoulos *et al.*, 1984; Tzonou *et al.*, 1984).]

Subsequently, Hartge *et al.* (1982) reported in a letter to the Editor of *The International Journal of Cancer* data on coffee and ovarian cancer collected as part of a case-control study of ovarian cancer (McGowan *et al.*, 1979). Cases were 158 women with pathologically confirmed primary ovarian cancer of the epithelial type treated in participating hospitals in the Washington DC area. Controls were 187 women frequency-matched to cases for age, race and hospital, treated at the same hospitals for conditions other than gynaecological, psychiatric or malignant diseases or pregnancy. Ten women had been excluded from the control series because they were hospitalized for conditions that might necessitate alterations in the diet. Women who regularly drank any amount of coffee had a nonsignificant increased risk for ovarian cancer compared to non-coffee drinkers (adjusted RR, 1.3; 95% CI, 0.8-2.2), but there was no statistically significant dose-response. [The

Working Group noted that there was no apparent confounding by the controlled variables in this study. The crude estimate of RR for drinkers of any amount of coffee was [1.3], i.e., identical to the reported adjusted figure.]

In a multicentre, hospital-based case-control study, Miller *et al.* (1984, 1987) collected data on 290 women, 20-69 years old, with epithelial ovarian cancer diagnosed within six months of the index hospital admission. Two control groups were used: women with benign conditions hospitalized more or less acutely (580) and women with malignancies (476) presumed to be unrelated to coffee (thus excluding women with pancreatic or bladder cancer) and to other factors that are considered to be predictive of ovarian cancer (thus excluding women with endometrial cancer). Women with benign conditions were *a priori* considered to be heavier consumers of coffee than the other control group (Miller *et al.*, 1984). There was no evidence of a positive association between ovarian cancer and drinking decaffeinated coffee. With respect to brewed coffee, there was evidence of a positive association with overall consumption when comparison was made with noncancer controls, but there was no such evidence when ovarian cancer cases were compared with the 'other cancers' control group. In no instance was there a clear indication of a dose-dependent trend. [The Working Group noted that, since the results with respect to the two control groups are contrary to what was predicted, it is legitimate to combine the two control groups, the results of which are given in Table 36. The crude estimate of RR for drinkers of any amount of coffee was [1.2]; from the crude and adjusted data, there seems to be no evidence of confounding.]

Byers *et al.* (1983) conducted a case-control study of dietary and nondietary factors in ovarian cancer. Cases were 274 white women, 30-79 years old, admitted to the Roswell Park Memorial Institute, Buffalo, NY, USA, between 1957-65 for ovarian cancer. Nineteen additional cases with ovarian tumours of nonepithelial origin and 36 additional cases with ovarian cancer diagnosed more than two years prior to the admission date were excluded. Controls were 1034 women, 30-79 years old [probably white only] admitted during the same period to the Institute for conditions that were found to be nonmalignant. An additional 499 women with diagnoses related to the reproductive system and 408 with conditions of the gastrointestinal system (401) or diabetes (seven) were excluded. There was no statistically significant association with any consumption category or dose trend with respect to coffee consumption. [The Working Group calculated that the age-adjusted RR for drinkers of any amount of coffee, with adjustment to age distribution of the control group by the direct method, was [1.2] (nonsignificant).]

In the Greek case-control study (Tzonou *et al.*, 1984), coffee consumption was compared between 150 women with epithelial ovarian cancer admitted to any of ten large hospitals in Athens between 1980 and 1981, and 250 control women hospitalized during the same period for fractures or orthopaedic disorders in the

Athens Hospital for Orthopaedic Disorders. In the final results, after adjustment for age, parity, menopausal status, age at menopause, use of exogenous oestrogens, tobacco smoking and consumption of alcoholic beverages, the χ^2 for trend in coffee consumption was 1.15 ($p \sim 0.27$); at no level of coffee consumption did the RR differ significantly from the value of 1.0. [The Working Group noted that the crude estimate of RR for drinkers of any amount of coffee was 1.2; comparison of crude and adjusted RR estimates indicates that there was little confounding, and that which existed was slightly 'negative'.]

Cramer *et al.* (1984) conducted a case-control study in the Boston, MA (USA), area between 1978 and 1981. Cases were 215 white women with newly diagnosed epithelial ovarian cancer admitted to 12 participating hospitals, whereas controls were 215 white women randomly selected from lists of Massachusetts residents, matched for age and precinct of residence. There was no evidence of an association between ovarian cancer and any of the combinations of coffee drinking, alcohol drinking or tobacco smoking. The crude RR was 1.2 for coffee drinkers. In the combinations that included coffee drinking, the RRs of coffee users *versus* nonusers of either coffee, alcohol or tobacco were between 1.2 and 1.8. [The Working Group noted that there was no evidence of overt confounding with respect to the results for coffee.]

La Vecchia *et al.* (1984) conducted a case-control study of ovarian cancer in Milan between 1979 and 1983. Cases were 247 women, 19-74 years of age, with epithelial ovarian cancer admitted to the university hospital and the National Cancer Institute of Milan. Controls were 494 women below the age of 75 years admitted to the university or general hospitals of the Milan area, suffering from diseases judged to be unrelated to coffee consumption or to any of the established or suspected risk factors of ovarian cancer. In the logistic regression analyses, there were statistically significant linear trends with daily consumption of coffee (p = 0.003) and with years of regular coffee consumption (p = 0.02). [The Working Group noted that comparison of crude [1.4] and adjusted RR indicates that there is some degree of confounding that incorrectly reduces the association between coffee consumption and risk of ovarian cancer ('negative' confounding).]

In a case-control study in the San Francisco Bay area, CA, USA, between 1983 and 1985, Whittemore *et al.* (1988) compared the exposure histories of 188 women with primary epithelial ovarian cancer admitted to one of seven participating hospitals with the exposure histories of women in two control groups. The first control group consisted of women hospitalized in one of the hospitals to which cases were admitted, whereas the second group was selected from the general population using random-digit dialling. When both control groups were combined, there was a statistically significant positive association between coffee drinking and the risk for ovarian cancer. [The Working Group noted that there may be an error, in that the

risk relative to the two control groups combined is higher (2.0) than that relative to either control group (1.9 for hospital controls and 1.5 for population controls).] RRs were elevated in 23 of the 24 categories of coffee drinking by quantity (cups per day), duration (years) or by product when hospital and population controls were considered separately; they were significantly elevated ($p < 0.05$) in 11 out of 12 such categories when hospital and population controls were combined. However, no clear trend was seen with daily quantity of coffee consumed.

Overall, in all seven case-control studies of coffee use and risk for ovarian cancer, users of any amount of coffee had an increased risk, although the elevation was significant in only two. In most of the studies, the increase was small or minimal: the overall crude RR estimates were between 1.1 and 1.3 in five studies, 1.4 in a recent study and 1.9 in the last one. Use of crude estimates is legitimate, since confounding of the association between coffee drinking and ovarian cancer in these sets was either absent or negative. In only one study was there a statistically significant dose-response relationship. A Mantel-Haenszel meta-analysis by the Working Group of the crude data from these seven studies (an acceptable, although slightly conservative procedure, for the reasons indicated above) gave a significant ($p < 0.01$) pooled estimated RR of [1.3 (95% CI, 1.1-1.5)] for coffee users *versus* nonusers.

(v) *Cancers of the digestive tract*

Case-control studies of cancers of the digestive tract and coffee consumption are summarized in Tables 37-39 (pp. 158, 162, 164).

Large bowel: Higginson (1966) studied 340 cases of colorectal cancer (196 male, 144 female) from seven hospitals in the Kansas City area, USA, from 1959 to the early 1960s. Three controls per case were selected from the same hospitals. Cases had histologically confirmed diagnoses, and controls excluded patients with gastrointestinal disease or with recent dietary abnormalities. Cases and controls were matched for age, sex and race. The socioeconomic status of cases and controls were similar. No significant association was found between coffee consumption and colorectal cancer: the RR for subjects who drank one or more cups of coffee a day was [0.8 (95% CI, 0.7-1.0)]. [The Working Group noted that no adjustment was made for confounding variables other than age, sex and race.]

Haenszel *et al.* (1973) studied 179 Japanese patients (101 male, 78 female) with colorectal cancer and 357 age- and sex-matched controls from the three largest general hospital in Honolulu, Hawaii, between 1966 and 1970. All but one of the cases had been confirmed histologically. Controls did not include patients with gastric or duodenal ulcers, gastrointestinal cancer or other diseases of the large bowel; their most frequent diagnoses were circulatory diseases, external causes and genito-urinary diseases. Patients were interviewed on dietary history, habits and

Table 36. Case–control studies of ovarian cancer (common epithelial tumours) and brewed coffee intake

Reference and location	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)			Comments
Hartge *et al.* (1982) USA	158, 187	0	1.0			Adjusted for age, gravity and smoking
		< 2	1.0 (0.5–2.2)			
		2–3	1.8 (0.9–3.6)			
		≥4	1.4 (0.6–3.0)			
Byers *et al.* (1983) USA	274, 1034	0	1.0			No significant association with any consumption category or trend
		< 3	[1.3]			
		≥3	[1.0]			
Miller *et al.* (1984, 1987) Several cities in the USA and Canada	287, 569/470		Noncancer controls	Cancer controls	All controls	Multivariate analysis
		0	1.0	1.0	1.0	
		1	1.6 (0.9–2.7)	1.0 (0.5–1.7)	[1.3]	
		2	1.5 (0.9–2.6)	0.9 (0.6–1.6)	[1.2]	
		3	1.6 (0.9–2.7)	0.9 (0.6–1.6)	[1.3]	
		4	1.7 (0.9–3.3)	1.6 (0.8–3.1)	[1.7]	
		≥5	1.1 (0.6–2.0)	1.0 (0.5–1.8)	[1.1]	
	289, 572/473	0	1.0	1.0	1.0	Decaffeinated coffee
		1–2	1.4 (0.9–2.2)	1.0 (0.6–1.4)	[1.2]	
		3–4	0.8 (0.4–1.6)	0.9 (0.5–1.6)	[0.9]	
		≥5	0.7 (0.2–2.1)	0.7 (0.2–3.3)	[0.7]	
Trichopoulos *et al.* (1981, 1984); Tzonou *et al.* (1984) Greece	149, 250	0	1.0			
		0.5–1	0.9			
		1.5–2	1.6			
		2.5–3	0.9			
		≥3.5	1.5			
Cramer *et al.* (1984) USA	215, 215	0	1.0			Adjusted for smoking
		Any	1.1			

Table 36 (contd)

Reference and location	Subjects (cases, controls)	Coffee consumption	Relative risk (95% CI)			Comments
La Vecchia *et al.* (1984) Italy	247, 494	0	1.0			Multivariate analysis
		≤1	1.5 (0.9–2.5)			
		2–3	1.9 (1.2–3.0)			
		≥4	2.2 (1.2–3.9)			
Whittemore *et al.* (1988) USA	188, 280/259		Hospital controls	Population controls	All controls	Adjusted for smoking
		0	1.0	1.0	1.0	
		1	2.2	1.9	2.4 (1.2–5.1)	
		2–3	2.1	1.6	2.3 (1.1–4.7)	
		≥4	2.0	1.6	2.1 (1.0–4.4)	
		0	1.0	1.0	1.0	
		1–14 years	1.6	0.7	1.5 (0.6–3.6)	
		15–24 years	1.8	1.7	2.2 (1.0–4.8)	
		25–39 years	2.4	1.7	2.3 (1.1–4.9)	
		≥40 years	3.5	2.5	3.4 (1.5–8.0)	

socioeconomic status. Coffee drinking was associated with a RR of 0.7, which was not statistically significant.

A significant negative association between coffee consumption and colon cancer was reported from case-control studies in Norway and the USA (Bjelke, 1973).

Graham *et al.* (1978) carried out a case-control study of white male patients with histologically confirmed cancer of the colon (256 patients) or rectum (330 patients) and 1222 controls seen at the Roswell Park Memorial Institute in Buffalo, NY, USA, during 1959-65. Controls were non-cancer, non-gastrointestinal patients who were selected so as to have a similar distribution as the cases, but no individual matching was carried out. Patients attending the hospital where the study was carried out were similar to the population of the neighouring areas in terms of socioeconomic and marital status, religion and smoking habits. The interview included demographic, socioeconomic and dietary variables. Frequent drinking of coffee was associated with a 'significant but small excess risk' for cancer of the colon but not of the rectum, as was 'drinking coffee very hot'. [The Working Group noted that no figures were given, that, other than for age, there was no adjustment for possible confounding variables and that no RRs or CIs are given.]

Dales *et al.* (1979) carried out a study of black patients with colorectal cancer and matched controls from hospitals and clinics in the San Francisco Bay area, CA, USA. Cases were identified from a cancer registry covering the period September 1973 to August 1976, but 60% could not be interviewed, mostly due to death or severe illness, leaving 99 cases. Similarly, only 50% (280) of the controls who were identified were successfully interviewed. The questionnaire was answered at the patients' homes and included demographic and socioeconomic data, as well as information on dietary habits three years prior to the interview. No association between coffee drinking and colorectal cancer was found. [The Working Group noted that the low rates of participation make this study difficult to interpret and that RRs associated with coffee consumption are not given.]

Watanabe *et al.* (1984) studied 65 cases of cancer of the rectum (39 male, 26 female) and 138 cases of colon cancer (71 male, 67 female) in Kyoto, Japan. For each case, one control was selected; the sex and age distribution of cases and controls were similar. Data were collected on a number of dietary items including coffee and tea consumption. No significant association was found between coffee drinking and cancer of the rectum or of the colon, although both risks were reduced by 20-30% among coffee drinkers.

Tajima and Tominaga (1985) compared the characteristics of 42 incident cases of colon cancer (27 male, 15 female) and 51 cases of rectal cancer (25 male, 26 female) with those of 186 controls admitted to a specialized hospital in Nagoya, Japan, between 1981 and 1983. The diagnoses of the cases were confirmed

histologically. There was no significant association between coffee drinking and either colon or rectal cancer (RRs for daily drinkers, 1.1 and 1.0, respectively). [The Working Group noted that almost half of the controls had gastrointestinal conditions.]

Macquart-Moulin *et al.* (1986) reported a case-control study from Marseille, France, based on 399 histologically confirmed cases of colorectal cancer and the same number of controls which was conducted between 1979 and 1984. After adjustment for age, sex, calories and weight, the risk in increasing quartiles of coffee consumption was 1.0, 0.6, 0.7 and 0.6. The test for trend was not significant.

Tuyns (1986) and Tuyns *et al.* (1988) presented the results of a study which covered approximately one-half of the cases of colorectal cancer in two Belgian provinces, Oost-Vlaanderen and Liège, in 1978-82. A total of 453 cases of colon cancer, 365 of rectal cancer and 2851 population controls were included. The response rate for controls was approximately 70%. The analyses were adjusted for age, sex and residence. 'Heavy consumers' of coffee and/or tea had crude RRs of 0.7 (95% CI, 0.6-0.9) for colon cancer and 0.8 for rectal cancer (0.6-0.9), relative to 'light consumers' (Tuyns, 1986). Separate results are not given for coffee and tea drinking, but the latter was reported to be rare.

In Yugoslavia, Jarebinski *et al.* (1989) compared 98 patients (56 male, 42 female) with histologically confirmed rectal cancer admitted to one of five hospitals in Belgrade in 1984-86 to two control groups: Hospital controls were patients admitted due to non-cancer conditions — mainly fractures and other injuries, cardiovascular diseases and hernias; a second control group consisted of neighbours of the cases. Controls were matched to cases by age, sex, place of residence and interviewer. The RRs associated with any coffee consumption were 1.7 when compared with hospital controls and 0.8 when compared with neighbourhood controls. The corresponding RRs for consumption of three or more cups per day were 1.1 and 0.8, and for having consumed coffee for 30 or more years, 1.2 and 1.2. None of these differences approached statistical significance. [The Working Group noted that no data are given on the proportions of potential cases or controls who could not be contacted.]

La Vecchia *et al.* (1988, 1989c) studied 455 histologically confirmed cases of colon cancer (221 male, 234 female), 295 cases of rectal cancer (170 male, 125 female) and 1944 hospital controls recruited from a network of teaching and general hospitals in greater Milan, Italy, between 1985 and 1988. Controls did not include patients with malignant tumours, digestive diseases or any condition related to use of coffee, alcohol or tobacco or which may have resulted in long-term dietary modification. RRs were calculated through logistic regression after adjustment for sex, age, social class, education, marital status, smoking and alcohol consumption. Compared to subjects consuming no to one cup per day, those consuming two cups

per day had a RR of 0.9 for colon cancer, and those consuming three or more cups had a RR of 0.6 (p for trend, < 0.01). The corresponding figures for rectal cancer were 1.0 and 0.7 (p for trend, < 0.05). The RRs were also examined after stratification for sex, age, marital status, education, social class, smoking and alcohol consumption. The overall pattern of protection afforded by coffee against colon cancer was evident in all strata but appeared to be restricted to males.

In another case-control study, carried out among Singapore Chinese, Lee *et al.* (1989) studied 203 (121 male, 82 female) consecutive incident cases (132 cases of colon cancer, 71 of rectal cancer) admitted to a general hospital in 1985-87. All cases had histologically confirmed colorectal cancer. A total of 426 controls were selected among 489 patients who were free of any gastrointestinal disease, cancer or diabetes; approximately two controls were selected for each case, matched for age group and sex. The response rates for cases and controls were above 80%. Coffee intake of one or more cups per day was associated with a nonsignificant 30-40% reduction in the risk for cancer at each site. When both sites were pooled, the association was close to significance ($0.1 > p > 0.05$). The effect of coffee remained virtually unchanged after adjustment for other food items for which a significant result was found. However, there was no evidence of a dose-response relationship.

Data on coffee consumption was collected as part of a multicentre, multiorgan case-control study in the USA (Rosenberg *et al.*, 1989). In 1978-82, data were obtained on coffee consumption one month before interview, whereas during 1983-86 the data on consumption were for one and three years before hospital admission. Cases were 717 patients with cancer of colon and 538 with rectal cancer, aged 30-69 years. A non-cancer control group consisted of 2128 trauma and 369 appendicitis patients, and a second, cancer control group was composed of 892 patients with malignant melanoma and 494 with lymphoma and bone cancer. Multiple logistic regression analyses, adjusting for age, sex, geographic area, year of interview, cigarette smoking, alcohol consumption, education, religion and race, were employed, using persons who consumed one cup of coffee per day as the referent category. For colon cancer, the adjusted RRs for drinking less than one, two and three to four cups of coffee per day compared to one cup per day were all close to one, but the risk associated with drinking five or more cups per day was significantly reduced (0.6; 95% CI, 0.4-0.8). This risk pattern was similar for men and women and when recent or past consumption was evaluated. For rectal cancer, the risks were close to unity for present or past consumption at all dose levels. The risk pattern was somewhat different for males and females: with the exception of a significantly elevated risk for drinking three to four cups per day (1.7; 95% CI, 1.0-2.8), men had nonsignificantly increased risks for all other dose categories; however, women had nonsignificantly reduced risks.

Benito *et al.* (1990) reported a case-control study of 286 incident cases of histologically confirmed colorectal cancer, 295 population controls and 203 hospital controls in Majorca, Spain. Coffee consumption was presented in quartiles. Risk in the lowest intake category was 1.0 and that in increasing quartiles of intake was 0.7, 0.5 and 0.8. The trend statistic was not significant.

Table 37. Summary of results of case–control studies on colorectal cancer and coffee consumption

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Higginson (1966) USA Colon and rectum	Men and women (340, 1020)	0/irregular < 1 < 2 ≥3	1.0 [0.4] [0.7] [0.6]	Crude RR; nonsignificant
Haenszel *et al.* (1973) USA Colon and rectum	Men and women (179, 357)	0 Any	1.0 0.7	Crude RR; nonsignificant
Watanabe *et al.* (1984) Japan				
Rectum	Men and women (65, 65)	0 Any	1.0 0.7 (0.3–1.6)	
Colon	Men and women (138, 138)	0 Any	1.0 0.8 (0.5–1.3)	
Tajima & Tominaga (1985) Japan				
Rectum	Men and women (51, 186)	0 Sometimes Daily	1.0 1.3 1.0	Nonsignificant; adjusted for age, sex
Colon	Men and women (42, 186)	0 Sometimes Daily	1.0 1.2 1.1	Nonsignificant; adjusted for age, sex
Macquart-Moulin *et al.* (1986) France Colon and rectum	Men and women (399, 399)	Quartiles Low 2nd 3rd High	 1.0 0.6 0.7 0.6	Nonsignificant; adjusted for age, sex, calories, weight

Table 37 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Tuyns *et al.* (1988) Belgium				
Rectum	Men and women (365, 2851)	Quartiles		Coffee and tea, but latter said to be uncommon; adjusted for age, sex, province; significant trend
		Low	1.0	
		2nd	0.9	
		3rd	0.9	
		High	0.7	
Colon	Men and women (453, 2851)	Quartiles		
		Low	1.0	
		2nd	0.9	
		3rd	1.0	
		High	0.6	
Jarebinski *et al.* (1989) Yugoslavia	Men and women (98, 98)	0	1.0	Nonsignificant; hospital controls
Rectum		Any	1.7	
		<3	1.0	Nonsignificant
		≥ 3	1.1	
		<30 years	1.0	Nonsignificant
		≥ 30 years	1.2	
		0	1.0	Nonsignificant; neighbourhood controls
		Any	0.8	
		<3	1.0	Nonsignificant
		≥ 3 cups/day	0.8	
		<30 years	1.0	Nonsignificant
		≥ 30 years	1.2	
La Vecchia *et al.* (1989c) Italy				
Rectum	Men (170, 1334)	0–1	1.0	$p < 0.01$ for men; nonsignificant for women; adjusted for age, marital status, education, social class, smoking, alcohol consumption; 95% CI could not be calculated; p levels based on chi-squared test for linear trend
		2	0.8	
		≥ 3	0.5	
	Women (125, 610)	0–1	1.0	
		2	1.2	
		≥ 3	0.9	

Table 37 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
La Vecchia *et al.* (1989c) (contd)				
Colon	Men (221, 1334)	0–1	1.0	$p < 0.05$
		2	0.8	
		≥3	0.6	
	Women (234, 610)	0–1	1.0	$p < 0.05$
		2	0.9	
		≥3	0.6	
Lee *et al.* (1989) Singapore				
Colon	Men and women (132, 426)	Tertiles		
		Low	1.0	
		Intermediate	0.7 (0.4–1.1)	Nonsignificant
		High	0.7 (0.4–1.2)	
Rectum	(71, 426)	Low	1.0	
		Intermediate	0.6 (0.3–1.1)	Nonsignificant
		High	0.7 (0.4–1.4)	
Colon and rectum	(203, 426)	Low	1.0	$0.1 > p > 0.05$; logistic analysis
		Intermediate	0.7 (0.4–1.0)	
		High	0.7 (0.5–1.1)	
Colon and rectum		Low	1.0	Nonsignificant; combined analysis; adjusted for cruciferous vegetables, total vegetables, meat/vegetable ratio, cholecystectomy history
		Intermediate	0.7 (0.4–1.0)	
		High	0.7 (0.5–1.2)	
Rosenberg *et al.* (1989) USA				Adjusted for age, sex, cigarette smoking, alcohol consumption,
Colon	Men and women (717, 3883)	< 1	1.1 (0.8–1.4)	several other potential confounding factors
		1	1.0	
		2	1.0 (0.8–1.3)	
		3–4	0.9 (0.7–1.2)	
		≥5	0.6 (0.4–0.8)	

Table 37 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Rosenberg *et al.* (1989) (contd)				
Rectum	(538, 3883)	< 1	1.2 (0.9–1.6)	
		1	1.0	
		2	1.1 (0.8–1.5)	
		3–4	1.1 (0.8–1.5)	
		≥5	1.2 (0.8–1.8)	
Benito *et al.* (1990)	Men and women	0	1.0	Nonsignificant; adjusted for age, sex, weight
Spain	(286, 498)	1–30/month	0.7	
Colon and rectum		31–60/month	0.5	
		≥60/month	0.8	

Stomach: In the study of Higginson (1966), described on p. 152, 93 cases of histologically confirmed stomach cancer and 279 age-, sex- and race-matched controls were studied. No significant association was found between coffee drinking and stomach cancer.

Graham *et al.* (1967) compared 276 cases (188 male, 88 female) of gastric cancer and 2221 controls (800 male, 1421 female) with non-neoplastic, non-digestive conditions seen at the Roswell Park Memorial Institute in Buffalo, NY, USA, between 1957 and 1965. Interviews on dietary habits prior to the onset of symptoms were carried out at admission. Separate analyses were made for each sex and for four age groups. The authors infer that the frequency of drinking coffee was not significantly associated with the risk for gastric cancer, but no figures were given.

Tajima and Tominaga (1985), in the study described above (p. 155), reported on 93 cases of histologically confirmed stomach cancer and 186 controls admitted to a specialized hospital in Nagoya, Japan. There was no significant association between coffee drinking and cancer of the stomach. [The Working Group noted that almost half of the controls had gastrointestinal conditions.]

Trichopoulos *et al.* (1985) studied 110 consecutive incident cases (57 male, 53 female) of histologically confirmed adenocarcinoma of the stomach admitted to two hospitals in Piraeus, Greece, between 1981 and 1984. Controls were 100 patients admitted to a nearby hospital due to accidents, fractures and orthopaedic disorders. Age, sex and years of schooling were controlled for in the statistical analysis. The association between the consumption of coffee and tea and the risk for stomach cancer was not statistically significant.

La Vecchia *et al.* (1989c) studied 397 histologically confirmed cases of stomach cancer (243 male, 154 female) and 1944 hospital controls from greater Milan, Italy. No association between coffee drinking and stomach cancer was found after adjustment for sex and age. The lack of association remained when the data were also adjusted for social class, education, marital status, smoking and alcohol consumption.

Table 38. Summary of results of case–control studies on stomach cancer and coffee consumption

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Higginson (1966) USA	Men and women (93, 279)	0/irregular <1 <2 ≥3	1.0 [0.7] [1.3] [1.3]	Crude RR; nonsignificant
Graham *et al.* (1967) USA	Men and women (276, 2221)			No association
Tajima & Tominaga (1985) Japan	Men and women (93, 186)	0 Not daily Daily	1.0 0.8 1.0	Nonsignificant; adjusted for age, sex
Trichopoulos *et al.* (1985) Greece	Men and women (110, 100)	1 (low) 2 3 4 5 (high)	1.0 [1.7] [1.8] [2.7] [3.2]	Nonsignificant after adjustment for age, sex, years of schooling; *p* values based on chi-squared test for linear trend; coffee and tea
La Vecchia *et al.* (1989c) Italy	Men and women (397, 1944)	0–1 2 ≥3	1.0 0.9 1.3	Nonsignificant; adjusted for age, marital status, education, social class, smoking, alcohol consumption; 95% CI could not be calculated; *p* values based on chi-squared test for linear trend

Upper digestive tract: Martinez (1969) studied 400 cases of cancer of the oesophagus (179 cases; 120 male, 59 female), mouth (153 cases; 115 male, 38 female) and pharynx (68 cases; 55 male, 13 female), comprising all histologically confirmed cases reported to the Puerto Rico cancer registry in 1966. For each case, three age- and sex-matched controls were selected: one non-cancer patient from the same hospital and two community controls. The results were presented for cancer of the mouth, pharynx and oesophagus taken together. For men, there was a significant association between drinking hot coffee and cancer at these three sites; there was a

similar, but nonsignificant trend for women. There was no association between drinking coffee with milk and the occurrence of cancer.

de Jong *et al.* (1974) carried out a hospital-based case-control study of oesophageal cancer among Singapore Chinese in 1970-72. For each case, four age- and sex-matched control patients were selected: two non-cancer patients from the same ward and two orthopaedic controls from a general hospital. Neither in the unadjusted analysis nor after adjustment for dialect group was there an association between coffee drinking and oesophageal cancer. Reported drinking of 'burning hot' coffee, however, was associated with a five- to six-fold higher crude risk of cancer. [The Working Group noted that the control groups included a large number of patients with digestive disorders.]

Yen *et al.* (1987) studied 67 patients with cancer of the extrahepatic bile ducts (40 men, 27 women) who had originally been recruited as controls in a case-control study of pancreatic cancer carried out in 11 large hospitals in Massachusetts and Rhode Island, USA, in 1975-79. The cases were obtained from a group of 104 patients with histologically confirmed cancer of the extrahepatic bile ducts, 37 of whom could not be interviewed. A control group was selected comprising 275 patients with other cancers not known to be related to tobacco or alcohol consumption — mainly of the breast (65 patients) and colon (60 patients). The analysis was stratified by age and sex. No association was found betweeen cancer occurrence and coffee drinking. [The Working Group noted that the study was not designed to study extrahepatic bile duct cancer, and a large proportion of the potential cases could not be interviewed.]

Victora *et al.* (1987), in a study described in detail in the monograph on mate, compared 171 cases of oesophageal cancer in southern Brazil with 342 hospital controls matched for age and sex. They found no effect of coffee drinking. [The Working Group noted that data are not given.]

In the study of La Vecchia *et al.* (1989c), described on p. 156, the association between coffee drinking and oesophageal cancer was examined by comparing 209 histologically confirmed cases (162 male, 47 female) with 1944 controls. The data were initially adjusted for age and sex, and later also for a number of confounding variables. Neither analysis showed any association. These authors also studied 50 cases of cancer of the mouth and pharynx (43 male, seven female) and 151 cases of liver cancer (115 male, 36 female). No association was found between coffee drinking and cancer of the mouth or pharynx, either in the analysis adjusted for sex and age or after adjustment for a number of confounding variables. In the first type of analysis, the RR for liver cancer for those drinking two cups per day was 0.7, and that for people drinking more than three cups per day, 0.6. This trend was less marked and no longer significant after adjustment for other confounding variables, when the corresponding RRs were 0.8 and 0.8.

Franco *et al.* (1989) carried out a case-control study of cancer of the mouth in three Brazilian cities. A total of 232 incident cases (201 male, 31 female) of histologically confirmed cancer of the tongue, gum, floor of the mouth and other parts of the oral cavity were recruited in three head-and-neck surgery services. Two hospital controls matched for age, sex, hospital and time of admission were selected for each case. Patients with cancer or with mental disorders were not included as controls. The crude analysis showed a clear trend of increasing risk with greater frequency of coffee drinking ($p = 0.01$). After adjustment for tobacco and alcohol consumption, however, this association was no longer significant. There was no indication that the temperature at which coffee was drunk affected the risk. [The Working Group noted that approximately one-third of the controls had digestive conditions.]

Table 39. Summary of results of case–control studies on other digestive cancers and coffee consumption

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Martinez (1969) Puerto Rico Oesophagus, mouth and pharynx	Men (290, 870)	0 Cold or warm Hot	1.0 [1.3] [2.7]	Black coffee; $p < 0.01$
		0 Cold or warm Hot	1.0 [0.8] [1.2]	With milk; non-significant
	Women (110, 330)	0 Cold or warm Hot	1.0 [1.6] [3.4]	Black coffee; non-significant
		0 Cold or warm Hot	1.0 [1.0] [1.6]	With milk; nonsignificant
de Jong *et al.* (1974) Singapore Oesophagus	Men (95, 465)	Not daily Daily Burning hot	1.0 0.9 5.1 crude RR 4.2 adjusted RR	Nonsignificant $p < 0.01$ for both
	Women (36, 200)	Not daily Daily Burning hot	1.0 1.4 6.6 crude RR 4.1 adjusted RR	Nonsignificant $p < 0.01$ for both; RR crude and adjusted for dialect group

Table 39 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Yen *et al.* (1987) USA Extrahepatic bile ducts	Men and women (67, 275)	0 Any 1–2 3–4 ≥5	1.0 0.8 (0.3–2.0) 0.8 (0.3–2.0) 1.0 (0.4–2.8) 0.6 (0.2–1.9)	Adjusted for age, sex
Victora *et al.* (1987) Brazil Oesophagus	Men and women (171, 342)			No association
La Vecchia *et al.* (1989c)				Nonsignificant; adjusted for age, sex, marital status, education, social class, smoking, alcohol consumption; 95% CI could not be calculated; *p* values based on chi-squared test for linear trend
Oesophagus	Men and women (209, 1944)	0–1 2 ≥3	1.0 0.9 1.0	
Mouth and pharynx	Men and women (50, 1944)	0–1 2 ≥3	1.0 0.9 0.8	
Liver	(151, 1944)	0–1 2 ≥3	1.0 0.8 0.8	
Franco *et al.* (1989) Brazil Oral cavity	Men and women (232, 464)	0–1 2–5 ≥6	1.0 1.3 (0.8–1.9) 1.9 (1.2–3.2)	$p = 0.01$; crude matched analysis; *p* value based on test for linear trend
		0–1 2–5 ≥6	1.0 1.1 (0.7–1.8) 1.5 (0.9–2.6)	Nonsignificant; adjusted for tobacco, alcohol consumption

(vi) *Cancers at other sites*

These studies are summarized in Table 40 (p. 166).

Henderson *et al.* (1976) studied 156 (105 male, 51 female) patients with *nasopharyngeal* squamous-cell *carcinoma* from three cancer registries and 267 controls in California, USA. From the main registry included in the study, 41% of the cases could not be interviewed. Controls were selected from inpatient and outpatient facilities and were matched to the cases for age, sex, race and socioeconomic status. No association was found between coffee drinking and nasopharyngeal carcinoma. [The Working Group noted that the description of the

selection of cases and controls is confusing, as several different sources were used, and that a high proportion of cases could not be interviewed.]

Mabuchi *et al.* (1985b) studied 149 patients with histologically confirmed *carcinoma of the vulva* from five metropolitan areas in the USA between 1972 and 1975. Cases were identified from more than 115 hospitals. One non-cancer patient was matched to each case according to age, race, marital status and hospital. Drinking one or more cups of coffee daily was associated with a doubling of the RR for cancer of the vulva, but this was not significant. The risk was significantly higher, however, among women drinking three or more cups per day. There was no dose-response relationship.

Mettlin (1989) reported a case-control study of 569 cases of histologically diagnosed *lung cancer* and the same number of controls who had no diagnosis or history of malignant or benign neoplasms, selected from patients seen at Roswell Park Memorial Institute in Buffalo, NY, USA. After adjustment for sex, smoking history, beta-carotene intake and education level relative to the risk in people who had never drunk coffee (1.0), the risk in increasing categories of coffee consumption was 1.0 (0.7-1.5) for less than one cup per day, 1.0 (0.7-1.4) for two to three cups per day and 1.3 (0.9-1.8) for four or more cups per day. The study also presented data regarding intake of decaffeinated coffee, and for the same categories of consumption the RRs were 1.0, 0.7 (0.5-0.9), 0.5 (0.3-0.7) and 0.8 (0.5-1.3).

In a case-control study of 208 cases of *non-Hodgkin's lymphoma* and 401 hospital controls in northeastern Italy, Franceschi *et al.* (1989) found a direct trend in risk, of borderline statistical significance, for coffee drinking in a multivariate analysis (RR for the upper tertile, 1.6). Only total methylxanthine-containing beverage consumption was correlated in multivariate analysis, which seemed to flatten out the relationship moderately.

Table 40. Summary of results of case–control studies on other cancers and coffee consumption

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk	Comments
Henderson *et al.* (1976) USA Nasopharynx	Men and women (156, 267)	0 Any	1.0 1.1	Nonsignificant; adjusted for sex, race, socioeconomic status, place of residence
Paffenbarger *et al.* (1978) USA				Case–control analysis of cohort study described on p. 118
Hodgkin's disease	Men (45, 180)	0 Any	1.0 2.5	Nonsignificant; matched analysis

Table 40 (contd)

Reference, location and site	Subjects (cases, controls)	Coffee consumption (cups/day)	Relative risk (95% CI)	Comments
Paffenbarger *et al.* (1978) (contd)				
Non-Hodgkin's lymphoma	Men (89, 356)	0 Any	1.0 1.6	Nonsignificant
Malignant melanoma	Men (45, 180)	0 Any	1.0 1.3	Nonsignificant
Lymphatic leukaemia	Men (27, 108)	0 Any	1.0 2.7	Nonsignificant
Myeloid leukaemia	Men (41, 164)	0 Any	1.0 3.2	$p = 0.02$
Other/unspecified leukaemias	Men (30, 120)	0 Any	1.0 0.8	Nonsignificant
Mabuchi *et al.* (1985b) USA Vulva	Women (149, 149)	< 1 1–2 3–4 ≥ 5	1.0 1.5 3.0 2.4	Unmatched analysis Nonsignificant $p < 0.05$ $p < 0.05$
Franceschi *et al.* (1989) Italy Non-Hodgkin's lymphoma	Men and women (208, 401)	Low Intermediate High	1.0 1.2 1.6	Borderline significance

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Coffee is a beverage that has been consumed in many parts of the world for centuries. The two main types of cultivated coffee are arabica and robusta. Green coffee is one of the major commodities of world trade and is exported mainly from tropical countries. Ground roasted coffee is brewed in many different ways, including decoction/boiling, infusion, filtration and percolation. Instant (soluble) coffee and decaffeinated coffee are more recent developments. Instant coffee is the dried pure water extract of ground roasted coffee and is used directly to prepare the beverage. Caffeine, the major pharmacologically active purine present in coffee, can be effectively and selectively removed from green coffee beans to give, ultimately, decaffeinated coffee.

Worldwide consumption of roasted coffee was estimated to be 4.3 million tonnes per year in 1983-87. Per-caput consumption in Nordic countries is two or three times higher than that in Canada, the USA and other countries of Europe. These regions have higher consumption levels than in the rest of the world.

Over 700 volatile compounds in many structural categories have been identified in roasted coffee, as well as numerous nonvolatile components (e.g., polysaccharides, melanoidins, protein-like products, chlorogenic acids). Arabica and robusta green coffees contain average caffeine levels of 1.2% and 2.2%, respectively, on a dry weight basis. Depending on the brewing method and species of coffee used, caffeine levels in the beverage are generally in the range of 70-150 mg per cup. Many volatile aldehydes and ketones have been characterized in coffee, including glyoxal and methylglyoxal. Occasional contamination of green coffees with mycotoxins has been reported.

4.2 Experimental carcinogenicity data

Coffee was tested for carcinogenicity in one study in mice and in two studies in rats by oral administration. The mice received instant coffee in the diet for their lifetime, including the gestation period; no increase in tumour incidence was reported. Rats were given brewed coffee as the drinking fluid in one study; a slight increase in the number of tumour-bearing animals was seen only among males in the lowest dose group. In another study, rats were given different samples of instant coffee, decaffeinated coffee or decaffeinated coffee supplemented with caffeine; no increase in tumour incidence was observed.

These three studies are suggestive of an absence of relationship between coffee and cancer in experimental animals, but the incomplete reporting of the study in mice precludes a definitive evaluation at present.

In a number of studies, various known carcinogens were administered by different routes either simultaneously or sequentially with coffee in water as the drinking fluid or in the diet. Several of these studies, however, suffered from various limitations and were not considered for the evaluation.

In one of the adequate studies, coffee reduced the number of pancreatic tumours per animal in azaserine-treated rats maintained on a high-fat diet; the result may have been due in part to impaired growth. No significant effect of coffee was found on the number of pancreatic tumours per animal induced in hamsters by *N*-nitrosobis(2-oxypropyl)amine. In separate experiments, rats on two different diets were treated intravenously or orally with a single dose of 7,12-dimethylbenz[*a*]anthracene in combination with coffee. No difference in the number of rats with mammary tumours was found as compared to animals receiving 7,12-dimethylbenz[*a*]anthracene only; a significant decrease in the number of

mammary tumours per animal was observed after administration of coffee only in rats treated intravenously and not in those treated orally with 7,12-dimethylbenz[*a*]anthracene.

4.3 Human carcinogenicity data

(*a*) *Descriptive studies*

The risk for cancer associated with coffee consumption has been investigated in several descriptive geographical and temporal studies. There was no consistent association between coffee intake, usually estimated indirectly from trade data, and cancer risk, although significant results were occasionally reported in a number of studies. Pancreatic cancer was correlated with coffee consumption in all of the studies in which the relationship was examined. None of the ecological studies showed an association with risk for bladder cancer.

(*b*) *Analytical studies*

(i) *All sites*

A cohort study in which a case-control analysis was used showed a nonsignificant reduction in risk for mortality from cancer at all sites with increased coffee consumption. A second cohort study with longer follow-up reported a nonsignificant increase in mortality after adjustment for age, smoking and other confounders.

(ii) *Bladder and urinary tract cancer*

Two cohort studies reported findings on bladder cancer incidence. In one, there was a nonsignificant increase in risk; the second showed neither an increase nor a decrease.

Of the 26 case-control studies considered that provided information on the possible relationship between coffee drinking and the occurrence of urinary tract cancers, predominantly of the bladder, in very different populations, 22 were used to make the evaluation. In 16 studies, a weak positive association was seen with consumption of coffee as compared to nonconsumption; in seven of these the association was significant, with a dose-response relationship in three. No association was seen in the six remaining studies. The association persisted, but was less clear, when reported nonsmokers were considered in seven of the 16 studies, suggesting that confounding by tobacco smoking is unlikely to be the sole explanation for this finding. The association was also found in men and women separately, suggesting that occupational factors could not fully explain the finding.

Of the four available case-control studies, three indicated a slightly increased risk for transitional-cell cancers of the renal pelvis and ureter, but none of the

results was significant. Six case–control studies and one cohort study do not provide evidence of a consistent association between adenocarcinoma of the kidney and coffee drinking.

Although drinking of decaffeinated coffee was addressed in six case–control studies, it was not possible to distinguish the effects from those of coffee containing caffeine.

Taken as a whole, these data are consistent with a weak positive relationship between coffee consumption and the occurrence of bladder cancer, but the possibility that this is due to bias or confounding cannot be excluded.

(iii) *Breast cancer*

None of the seven case–control studies has suggested the existence of an association between breast cancer risk and the consumption of coffee. All of the studies gave relative risk estimates that were near unity. One study presented results on instant coffee separately and also found no association; three studies showed no association with decaffeinated coffee consumption. Confounding due to recognized risk factors for breast cancer was controlled in most studies. There is no reason to believe that measurement error or confounding was responsible for the finding.

(iv) *Cancer of the large bowel*

Cohort studies that addressed the issue of coffee drinking and risk for cancer of the colon or rectum were not particularly informative but have generally been interpreted as showing no association.

Of the 12 informative case–control studies, 11 indicated inverse ('protective') associations between coffee consumption and risk for colorectal cancer, which reached significance in five. A significant dose–response relationship was seen in one study. At present, it is not possible to exclude bias and confounding as the source of the apparent inverse association, but the collective evidence is also compatible with a 'protective' effect.

(v) *Pancreatic cancer*

Six cohort studies provide data on the relationship between coffee consumption and pancreatic cancer. None reported a significant association with increased consumption; any nonsignificant increase was reduced following adjustment for smoking.

Twenty–one case–control studies have reported on the relationship between coffee consumption and pancreatic cancer. An early report showed a positive relationship, with a significant dose–response, in women but not in men, which persisted after removing those controls with digestive disorders. Another study

reported a significant relationship with decaffeinated coffee but not with consumption of all kinds of coffee. Nineteen subsequent reports have been less positive overall. In ten of these studies, a positive association was seen; in three of these, the findings were significant, with a dose–response relationship in two studies. No association was seen in seven studies, and a weakly negative association was found in another. A nonsignificant increase in risk for the highest exposure group has been a more consistent finding, but this has generally become weaker after adjustment for smoking and may be the result of residual confounding. Potential biases associated with the comparability of case and control groups also complicate interpretation, and methodological problems were noted in some studies.

Taken as a whole, the data are suggestive of a weak relationship between high levels of coffee consumption and the occurrence of pancreatic cancer, but the possibility that this is due to bias or confounding is tenable.

The results with regard to decaffeinated coffee are less comprehensive but have generally been negative.

(vi) *Ovarian cancer*

In two case–control studies of coffee drinking and risk for ovarian cancer, a significant increase in risk was found, whereas in five others small, nonsignificant increases were noted. An overall analysis of the data indicates a marginal, significant increase in relative risk, but bias from unidentified sources or even chance cannot be ruled out.

The few available studies do not suggest that drinking decaffeinated coffee increases the risk for ovarian cancer.

(vii) *Gastric cancer*

The relationship between coffee drinking and gastric cancer was studied in five case–control investigations, none of which showed an association.

(viii) *Cancers of the upper digestive tract*

Six case–control studies assessed the association between coffee drinking and cancers of the oesophagus, mouth and pharynx. After adjustment for confounding variables, the frequency of coffee drinking was not associated with risk for cancer in any of these studies. Overall, no association was found between coffee drinking and cancers of the upper digestive tract, except when populations who drink coffee at very high temperatures were studied.

(ix) *Cancers at other sites*

In one case–control study, no association with the occurrence of liver cancer was found among coffee drinkers after adjustment for smoking and alcohol consumption.

Two cohort studies and one case–control study showed no association with lung cancer.

A cohort study reported associations between coffee drinking and Hodgkin's disease and lymphatic and myeloid leukaemia; no association was reported with the occurrence of non–Hodgkin's lymphoma, malignant melanoma, or other and unspecified leukaemias. One case–control study showed an increased incidence of carcinoma of the vulva among coffee drinkers. A single cohort study showed an association with cervical cancer.

4.4 Other relevant data

(*a*) *Toxic effects*

The available evidence cannot be used to establish a significant, independent relationship between coffee consumption and morbidity or mortality from coronary heart disease. The question remains open, however, especially in view of the finding that some methods of coffee preparation are associated with an elevation in plasma levels of cholesterol and low–density lipoproteins.

(*b*) *Effects on reproduction and prenatal toxicity*

The teratogenic potential of coffee and caffeine–containing beverages was investigated in two cohort and four case–control studies. Two studies (one cohort and one case–control) found significant positive associations between the consumption of caffeine–containing drinks and the risk for malformations. The remaining four studies (one cohort and three case–control), which included the three most informative reports, failed to find an association. Taken together, these studies do not provide evidence of a teratogenic effect of coffee intake.

Eight studies, from Costa Rica, the Federal Republic of Germany, the UK and the USA, reported an association between decreased birth weight and intake of coffee and caffeine–containing beverages, which was statistically significant in the crude analyses. After correction for confounding variables, including smoking, four of the studies reported positive associations which were significant. Of two other studies, one reported an increased risk among heavy consumers which, however, was not significant, and the other reported a positive association of only borderline significance. The two remaining studies did not show an association after adjustment for confounding. Reporting of coffee consumption was usually most complete for the first and second trimesters, while the greatest impact on birth

weight may be from consumption during the last trimester. Overall, the data provide an indication that maternal coffee drinking reduces the birth weight of offspring.

Of the three studies with adequate design and interpretation, only one showed a clear dose–response relationship.

Information concerning prematurity was insufficient for conclusions to be drawn about an effect of coffee consumption. One study provided evidence of a relationship between late spontaneous abortions and moderate to heavy coffee consumption.

No effect on reproduction was observed in rats given percolated or drip (filtered) coffee as the drinking fluid. Developmental delays were observed in the offspring of coffee-treated rats, including decreased fetal and neonatal body weights and delayed ossification. No teratogenic effect was observed.

No teratogenic effect or effect on reproduction was observed in rats given instant coffee as the drinking fluid or as crystals in the diet. In the offspring of treated rats, delayed development was observed, including decreased fetal and neonatal body weight and delayed ossification shortly before birth.

No teratogenic effect or effect on reproduction was observed in rats given decaffeinated coffee (either brewed or instant) as the drinking fluid, although a decrease in body weight of offspring was observed.

The reproductive effects seen in these studies occurred only at levels of coffee much higher than those to which humans are exposed.

(*c*) *Genetic and related effects*

Otherwise healthy splenectomized coffee drinkers, some of whom occasionally drank tea, had an increased frequency of micronuclei in both reticulocytes and mature erythrocytes.

The urine of coffee drinkers was not mutagenic to bacteria but induced chromosomal aberrations in cultured mammalian cells.

Brewed coffee induced chromosomal aberrations and sister chromatid exchange in cultured human lymphocytes. Sister chromatid exchange was also induced in cultured mammalian cells. In insects, negative results were obtained for aneuploidy, chromosomal aberrations, dominant lethal effects and sex-linked recessive lethal mutation; brewed coffee gave weakly positive results in assays for somatic cell mutation and mitotic recombination. In bacteria, it was mutagenic, particularly to strains with enhanced sensitivity to oxidative mutagens, and induced DNA damage.

Instant coffee did not induce sister chromatid exchange or micronuclei in the bone-marrow cells of rodents treated *in vivo*. It induced chromosomal aberrations in cultured human lymphocytes and induced mutations and sister chromatid

exchange in cultured mammalian cells. In insects, negative results were obtained for aneuploidy, chromosomal aberrations, dominant lethal effects and sex-linked recessive lethal mutations; instant coffee gave weakly positive results in assays for somatic cell mutation and mitotic recombination. In bacteria, instant coffee was mutagenic, particularly to strains sensitive to oxidative mutagens, and induced DNA damage; it was not mutagenic in host-mediated bacterial mutagenicity assays.

Decaffeinated coffee induced chromosomal aberrations in cultured human lymphocytes and sister chromatid exchange in cultured mammalian cells. It gave negative results in assays for somatic cell mutation and mitotic recombination assays in insects. In bacteria, decaffeinated coffee was mutagenic, particularly in strains with enhanced sensitivity to oxidative mutagens, and induced DNA damage.

Coffee reduced the genotoxic activity of several model mutagens both *in vivo* and *in vitro*.

4.5 Evaluation[1]

There is *limited evidence* in humans that coffee drinking is carcinogenic in the urinary bladder.

There is *evidence suggesting lack of carcinogenicity* of coffee drinking in the human female breast and in the large bowel.

There is *inadequate evidence* in humans that coffee drinking is carcinogenic in the pancreas, ovary and other body sites.

There is *inadequate evidence* in experimental animals for the carcinogenicity of coffee.

Overall evaluation[2,3]

Coffee is *possibly carcinogenic to the human urinary bladder (Group 2B)*.

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[1]For description of the italicized terms, see Preamble, pp. 27–31.

[2]There is some evidence of an inverse relationship between coffee drinking and cancer of the large bowel; coffee drinking could not be classified as to its carcinogenicity to other organs.

[3]M.J. Arnaud dissociated himself from the overall evaluation.

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