

# Effects of caffeine on human health

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*Caffeine is probably the most frequently ingested pharmacologically active substance in the world. It is found in common beverages (coffee, tea, soft drinks), in products containing cocoa or chocolate, and in medications. Because of its wide consumption at different levels by most segments of the population, the public and the scientific community have expressed interest in the potential for caffeine to produce adverse effects on human health. The possibility that caffeine ingestion adversely affects human health was investigated based on reviews of (primarily) published human studies obtained through a comprehensive literature search. Based on the data reviewed, it is concluded that for the healthy adult population, moderate daily caffeine intake at a dose level up to 400 mg day<sup>-1</sup> (equivalent to 6 mg kg<sup>-1</sup> body weight day<sup>-1</sup> in a 65-kg person) is not associated with adverse effects such as general toxicity, cardiovascular effects, effects on bone status and calcium balance (with consumption of adequate calcium), changes in adult behaviour, increased incidence of cancer and effects on male fertility. The data also show that reproductive-aged women and children are 'at risk' subgroups who may require specific advice on moderating their caffeine intake. Based on available evidence, it is suggested that reproductive-aged women should consume  $\leq 300$  mg caffeine per day (equivalent to 4.6 mg kg<sup>-1</sup> bw day<sup>-1</sup> for a 65-kg person) while children should consume  $\leq 2.5$  mg kg<sup>-1</sup> bw day<sup>-1</sup>.*

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tal malformations, development, fertility, foetal growth, pregnancy, spontaneous abortion, tea

## Introduction

Caffeine (1,3,7-trimethylxanthine) is a natural alkaloid found in coffee beans, tea leaves, cocoa beans, cola nuts and other plants. It is probably the most frequently ingested pharmacologically active substance in the world, found in common beverages (coffee, tea, soft drinks), products containing cocoa or chocolate, and medications, including headache or pain remedies and over-the-counter stimulants (Murphy and Benjamin 1981, IARC 1991b, Dlugosz and Bracken 1992, Carrillo and Benitez 1996).

The possibility that caffeine consumption can have adverse effects on human health was assessed based on the results of (primarily) published human studies obtained through a comprehensive literature search. The results of this assessment are summarized here.

## Sources and prevalence of caffeine consumption

In North America, coffee (60–75%) and tea (15–30%) are the major sources of caffeine in the adult diet, whereas caffeinated soft drinks and chocolate are the major sources of caffeine in the diet of children. Coffee is also the primary source of caffeine in the diet of adults in some European countries, such as Finland, Sweden, Denmark and Switzerland. Brewed coffee contains the most caffeine (56–100 mg/100 ml), followed by instant coffee and tea (20–73 mg/100 ml) and cola (9–19 mg/100 ml). Cocoa and chocolate products are also important sources of caffeine (e.g. 5–20 mg/100 g in chocolate candy), as are a wide variety of both prescription (30–100 mg/tablet or capsule) and non-prescription (15–200 mg/tablet or capsule) drugs (Dlugosz and Bracken 1992, Barone and Roberts 1996, Shils *et al.* 1999, Tanda and Goldberg 2000).

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In Canada, published values for the average daily intake of caffeine from all sources is about  $2.4 \text{ mg kg}^{-1}$  body weight (bw) for adults and  $1.1 \text{ mg kg}^{-1}$  bw for children 5–18 years old (Chou 1992). Recently, Brown *et al.* (2001) reported daily caffeine intakes ranging from 288 to 426 mg (equivalent to  $4.5\text{--}6.5 \text{ mg kg}^{-1}$  bw in a 65-kg person) in the adult population (481 men and women aged 30–75 years) residing in southern Ontario, Canada. Elsewhere, mean daily caffeine intake for adults among the general population has been given as approximately  $3 \text{ mg kg}^{-1}$  bw in the USA,  $4 \text{ mg kg}^{-1}$  bw in the UK and  $7 \text{ mg kg}^{-1}$  bw in Denmark. For high-level consumers, daily intakes range from 5 to  $15 \text{ mg kg}^{-1}$  bw. For children, daily caffeine intakes have been given as  $1 \text{ mg kg}^{-1}$  bw in the USA,  $<3 \text{ mg kg}^{-1}$  bw in the UK and  $<2.5 \text{ mg kg}^{-1}$  bw in Denmark (IARC 1991b, Ellison *et al.* 1995, Barone and Roberts 1996, Hughes and Oliveto 1997).

Note that the caffeine content of coffee and tea is dependent on their method of preparation and the product brand. In addition, variations in caffeine intake can occur due to differences in the size of the serving 'cup' (Stavric *et al.* 1988). The impact of these variations should be considered in the interpretation and comparison of clinical studies, particularly when cultural differences may be involved.

### Pharmacokinetics

Following ingestion, caffeine is rapidly and essentially completely absorbed from the gastrointestinal tract into the bloodstream. Maximum caffeine concentrations in blood are reached within 1–1.5 h following ingestion. Absorbed caffeine is readily distributed throughout the entire body. It passes across the blood–brain barrier, through the placenta into amniotic fluid and the foetus, and into breast milk. Caffeine has also been detected in semen (Berger 1988, Arnaud 1999).

The liver is the primary site of caffeine metabolism (Stavric and Gilbert 1990, Arnaud 1999). In adults, caffeine is virtually completely metabolized to 1-methylxanthine and 1-methyluric acid from the paraxanthine intermediate. Only 1–5% of ingested caffeine is recovered unchanged in the urine. Infants up to the age of 8–9 months have a greatly reduced ability to metabolize caffeine, excreting about 85%

of the administered caffeine in the urine unchanged (Nolen 1989, Stavric and Gilbert 1990).

The elimination half-life of caffeine ranges between 3 and 7 h and can be influenced by many factors, including sex, age, use of oral contraceptives, pregnancy and smoking. Caffeine's half-life has been reported to be 20–30% shorter in females than in males. The half-life in newborns ranges from 50 to 100 h, but it gradually approaches that of an adult by 6 months of age. The half-life in females using oral contraceptive steroids is approximately twice that observed for ovulatory females. During pregnancy, the metabolic half-life increases steadily from 4 h during the first trimester to 18 h during the third trimester. Cigarette smoking is associated with about a twofold increase in the rate at which caffeine is eliminated (Aranda *et al.* 1979, Dalvi 1986, Gilbert *et al.* 1986, Stavric and Gilbert 1990, James 1991a, Dlugosz and Bracken 1992, Eskenazi 1993, Hinds *et al.* 1996, Arnaud 1999, Karen 2000).

### General toxicity

Death due to excessive caffeine ingestion is not common, and only a few cases have been reported in the literature. The acute lethal dose in adult humans has been estimated to be 10 g/person. Death has been reported after ingestion of 6.5 g caffeine, but survival of a patient who allegedly ingested 24 g caffeine was also reported (Stavric 1988, James 1991b).

Caffeine toxicity in adults can present a spectrum of clinical symptoms, ranging from nervousness, irritability and insomnia to sensory disturbances, diuresis, arrhythmia, tachycardia, elevated respiration and gastrointestinal disturbances. Caffeine toxicity in children is manifested by severe emesis, tachycardia, central nervous system agitation and diuresis. Chronic exposure to caffeine has been implicated in a range of dysfunctions involving the gastrointestinal system, liver, renal system and musculature (Stavric 1988, James 1991b).

The most important mechanism of action of caffeine is the antagonism of adenosine receptors. Adenosine is a locally released purine which acts on different receptors that can increase or decrease cellular concentrations of cyclic adenosine monophosphate (cAMP). Caffeine selectively blocks adenosine receptors and competitively inhibits the action of adeno-

sine at concentrations found in people consuming caffeine from dietary sources. Caffeine results in the release of norepinephrine, dopamine and serotonin in the brain and the increase of circulating catecholamines, consistent with reversal of the inhibitory effect of adenosine (Benowitz 1990).

It is now widely believed that habitual daily use of caffeine >500–600 mg (four to seven cups of coffee or seven to nine cups of tea) represents a significant health risk and may therefore be regarded as 'abuse'. Sustained abuse may in turn result in 'caffeinism', which refers to a syndrome characterized by a range of adverse reactions such as restlessness, anxiety, irritability, agitation, muscle tremor, insomnia, headache, diuresis, sensory disturbances (e.g. tinnitus), cardiovascular symptoms (e.g. tachycardia, arrhythmia) and gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea) (James and Paull 1985).

Excessive caffeine intake (>400 mg day<sup>-1</sup>) may increase the risk of detrusor instability (unstable bladder) development in women. For women with pre-existing bladder symptoms, even moderate caffeine intake (200–400 mg day<sup>-1</sup>) may result in an increased risk for detrusor instability (Arya *et al.* 2000).

### Cardiovascular effects

Clinical studies have investigated the effects of caffeine or coffee on cardiac arrhythmia, heart rate, serum cholesterol and blood pressure. Epidemiological studies have largely focused on the association between coffee intake and cardiovascular risk factors, including blood pressure and serum cholesterol levels, or the incidence of cardiovascular disease itself.

Clinical studies have shown that single doses of caffeine <450 mg do not increase the frequency or severity of cardiac arrhythmia in healthy persons, patients with ischaemic heart disease or those with serious ventricular ectopia (Myers 1998). Studies conducted in healthy or hypertensive subjects suggest that when a change in heart rate is observed, it is typically a decrease at doses >150 mg/person (James 1991c, Green *et al.* 1996, Myers 1998). The rapid development of tolerance to the heart rate effect of caffeine (Green *et al.* 1996) complicates data interpretation. The generally modest decrease in heart rate is likely not clinically relevant (Myers 1998).

Several clinical and epidemiological studies have suggested that coffee consumption is associated with significant increases in total and low-density lipoprotein cholesterol levels. Recent studies, however, suggest that it is not the caffeine in coffee that is responsible for its hypercholesterolaemic effect (Thelle *et al.* 1987, James 1991c, d, Thelle 1993, 1995, Gardner *et al.* 1998). Two diterpenoid alcohols, cafestol and kahweol, found at significant levels in boiled coffee have been identified as hypercholesterolaemic components. Although these components are largely trapped by the use of a paper filter in coffee preparation, there is some evidence that consumption of filtered coffee is associated with small increases in serum cholesterol levels (Thelle 1995).

The effect of caffeine on blood pressure in habitual caffeine consumers and abstainers has been investigated in more than 50 acute and 19 repeated-dose clinical trials with healthy or hypertensive subjects (reviewed by Myers 1988, 1998, James 1991c, Green *et al.* 1996). The results of the acute studies indicate that caffeine induces an increase in systolic (5–15 mmHg) and/or diastolic (5–10 mmHg) blood pressure, most consistently at doses >250 mg/person, in adults of both sexes, irrespective of age, race, blood pressure status, or habitual caffeine intake. The effect is most pronounced in elderly, hypertensive or caffeine-naïve individuals. The pressor effect of caffeine was also observed in many of the repeated-dose studies, but not as consistently as in the acute studies. It is generally agreed that tolerance to these pressor effects develops within 1–3 days, but is partially lost after abstinence for as little as 12 h. The clinical significance of caffeine's pressor effects and the development of tolerance continues to be discussed in the literature (James 1991c, Green *et al.* 1996, Myers 1998).

Epidemiological studies investigating associations between caffeine and blood pressure (reviewed by Myers 1988, 1998, James 1991c, 1997, Green *et al.* 1996) have yielded conflicting results (i.e. positive, negative or no association). These inconsistencies may reflect methodological problems, including misclassification resulting from the use of dietary recall data, tolerance to the pressor effects of caffeine and the effect of smoking on the plasma half-life of caffeine. While James (1991c, 1997) and Green *et al.* (1996) indicated that further research was needed, Myers (1998) concluded that there was no epidemiological evidence to support any relationship between caffeine use and blood pressure.

Epidemiological studies addressing the possible association between consumption of caffeine-containing beverages, usually coffee, and coronary heart disease include case-control, longitudinal cohort and prospective studies (reviewed by James 1991d, Lynn and Kissinger 1992, Myers and Basinski 1992, Franceschi 1993, Thelle 1995, Myers 1998); meta-analyses of case-control and/or prospective study data were published by Greenland (1987, 1993) and Kawachi *et al.* (1994); and a recent case-control was published by Palmer *et al.* (1995) and two recent prospective studies were published by Stensvold and Tverdal (1995) and Hart and Smith (1997). Most relied on self-administered questionnaires to determine intakes of caffeinated beverages. Cardiovascular disease was assessed by a variety of outcome variables, including death from myocardial infarction or coronary heart disease, non-fatal myocardial infarction or coronary event, angina pectoris and/or hospitalization for coronary heart disease. The results of both case-control and prospective epidemiological studies yielded inconsistent results, although case-control studies were more likely to show a significant relationship between coffee consumption and cardiovascular disease, with an increased risk generally observed at intakes of five or more cups of coffee per day ( $\geq 500$  mg caffeine day<sup>-1</sup>). Longitudinal cohort studies published from 1986 yielded more consistent positive associations than those published up to 1981 (Greenland 1993). The inconsistencies both within and between case-control and prospective studies have resulted in controversies regarding study methodologies and data interpretation (James 1991d, Myers and Basinski 1992, Franceschi 1993, Greenland 1993, Myers 1998). While recognizing the ambiguity of the epidemiological data, Greenland (1993) and Franceschi (1993) concluded that the possibility of heavy coffee consumption (defined as 10 or more cups per day by Greenland 1993; probably four or more cups per day in Franceschi 1993) adversely affecting the incidence of coronary heart disease or mortality cannot be ruled out.

None of the epidemiological data determine whether it is caffeine *per se* or other components of coffee that are responsible for coffee's association with cardiovascular disease. Although no significant association has been found between tea consumption and cardiovascular disease (Franceschi 1993, Thelle 1995, Myers 1998), it has been suggested that the beneficial effects of the flavonoids present in tea may offset any adverse effect of caffeine (Thelle 1995). Support for the idea that caffeine in coffee is not responsible for

cardiovascular effects comes from epidemiological studies showing an increased risk of coronary events with consumption of decaffeinated coffee (Grobbee *et al.* 1990, Gartside and Glueck 1993).

In summary, the data currently available indicate that moderate caffeine intake (four or fewer cups of coffee per day, or  $\leq 400$  mg caffeine day<sup>-1</sup>) does not adversely affect cardiovascular health. There are insufficient epidemiological data to draw any conclusions about the risk for coronary heart disease or mortality associated with consumption of 10 or more cups of coffee per day ( $\geq 1000$  mg caffeine day<sup>-1</sup>).

### Effects on bone and calcium balance

The database on caffeine's potential to adversely influence bone metabolism includes epidemiological studies investigating the relationship between caffeine and/or coffee intake and the risk of osteoporosis as characterized by low bone mineral density and increased susceptibility to fractures, as well as metabolic studies examining the effect of caffeine on calcium homeostasis.

Caffeine intake of 150–300 mg after a 10-h fast increased urinary calcium excretion 2–3 h after exposure in adolescent men and women (Massey and Hollingbery 1988), women 22–30 years of age (Massey and Wise 1984, Massey and Opryszek 1990), men 21–42 years of age (Massey and Berg 1985), and women 31–78 years of age consuming  $\geq 200$  mg caffeine day<sup>-1</sup> (Bergman *et al.* 1990). Tolerance to the renal effects of caffeine does not develop, as habitual coffee intake had no effect on the increase in calcium excretion associated with an acute caffeine dose (Massey and Opryszek 1990). Caffeine-induced hypercalciuria was not affected by oestrogen status (Bergman *et al.* 1990), gender or age (Massey and Wise 1992). Barger-Lux *et al.* (1990) reported that caffeine intakes of 400 mg person<sup>-1</sup> day<sup>-1</sup> for 19 days led to evidence of altered bone remodelling in healthy premenopausal women between the ages of 35 and 44, but had no effect on fractional calcium absorption, endogenous faecal calcium or urinary calcium excretion. An earlier study in the same population suggested that caffeine consumption of 175 mg person<sup>-1</sup> day<sup>-1</sup> was positively associated with increased 24-h urinary calcium excretion (Heaney and Recker 1982).

Whether it is through increased urinary calcium excretion (Massey and Whiting 1993) or decreased intestinal calcium absorption (Heaney 1998), caffeine does appear to have a negative effect on calcium balance (Hasling *et al.* 1992, Barger-Lux and Heaney 1995). Barger-Lux *et al.* (1990) concluded that a daily intake of 400 mg caffeine by healthy premenopausal women with a calcium intake of at least 600 mg day<sup>-1</sup> has no appreciable effect on calcium excretion. Hasling *et al.* (1992) derived a model from data collected from postmenopausal women that indicated coffee intakes >1000 ml day<sup>-1</sup> (760 mg caffeine day<sup>-1</sup>) could induce excess calcium loss, while intakes of 150–300 ml coffee day<sup>-1</sup> (112–224 mg caffeine day<sup>-1</sup>) would have little impact on calcium balance. The biological significance of caffeine's negative effect on calcium balance has been debated (Barger-Lux *et al.* 1990, Massey and Whiting 1993).

Several epidemiological studies have been conducted to assess the relationship between caffeine intake and bone density. Increasing caffeine intakes were not associated with significant decreases in bone density in adolescent women (Lloyd *et al.* 1998), young women 20–30 years of age (Eliel *et al.* 1983, McCulloch *et al.* 1990, Packer and Recker 1996, Conlisk and Galuska 2000), premenopausal women (Picard *et al.* 1988, Lacey *et al.* 1991, Lloyd *et al.* 1991, Hansen 1994), perimenopausal women (Slemenda *et al.* 1987, 1990), postmenopausal women (Slemenda *et al.* 1987, Hansen *et al.* 1991, Reid *et al.* 1994, Lloyd *et al.* 1997, 2000, Hannan *et al.* 2000) or men (Eliel *et al.* 1983, Glynn *et al.* 1995, Hannan *et al.* 2000). Some negative associations between caffeine intake and bone density have been observed; these associations disappeared when confounders such as calcium intake were adjusted for in some studies (Cooper *et al.* 1992, Johansson *et al.* 1992), but not others (Hernández-Avila *et al.* 1993). Some researchers have found that caffeine's effects on bone density were dependent on calcium intakes. Harris and Dawson-Hughes (1994) concluded that two to three servings of coffee (280–420 mg caffeine day<sup>-1</sup>) may accelerate bone loss in healthy postmenopausal women with calcium intakes <800 mg day<sup>-1</sup>. Barrett-Connor *et al.* (1994) found that only postmenopausal women who did not report drinking at least one glass of milk per day between the ages of 20 and 50 years exhibited a coffee-associated decrease in bone mineral density.

Caffeine intake has been investigated as a potential risk factor for bone fracture, the major cause of

morbidity and mortality associated with osteoporosis. In case-control studies, caffeine intakes were not associated with an increased risk of hip fracture in women >55 years of age (Nieves *et al.* 1992), women 18–70 years of age (Tavani *et al.* 1995), or men or women >65 years of age (Cumming and Klineberg 1994). In a cross-sectional study, Travers-Gustafson *et al.* (1995) were also unable to show that caffeine intakes were related to an increased incidence of low-trauma fractures. In contrast, data from the Nurses Health Study found that women who consumed more than four cups of coffee per day (>544 mg caffeine day<sup>-1</sup>) had a higher risk of hip fracture than those who 'almost never' consumed coffee (Hernández-Avila *et al.* 1991). Although other studies have shown an increase in the risk of hip fracture with dietary caffeine, it was not clear whether the analysis adjusted for differences in calcium intake (Holbrook *et al.* 1988) or whether calcium intake data were unavailable (Kiel *et al.* 1990).

Interpretation of caffeine's effects on bone metabolism are complicated because coffee intake is associated with other risk factors for osteoporosis: calcium intake (Heaney and Recker 1982, Massey and Hollingbery 1988, Hasling *et al.* 1992, Hernández-Avila *et al.* 1993), age (Barger-Lux and Heaney 1995), cigarette smoking (Cooper *et al.* 1992, Johansson *et al.* 1992, Barrett-Connor *et al.* 1994) and alcohol consumption (Cooper *et al.* 1992, Barrett-Connor *et al.* 1994). Collectively, the available data suggest that an increased caffeine intake is associated with a slight but biologically real deterioration in calcium balance. The majority of evidence indicates that this effect is through caffeine-induced hypercalciuria. The biological significance of caffeine's negative effect on calcium balance continues to be the topic of scientific debate, as studies on both bone density and fracture risk have revealed conflicting results. Bruce and Spiller (1998) suggest that a lifetime pattern of high caffeine intake (more than four cups of coffee per day or >400 mg caffeine day<sup>-1</sup>) in women contributes to a negative impact on calcium and bone metabolism and is correlated with bone loss or fracture risk, particularly when there is a low calcium intake. Heaney (1998) suggests that the epidemiological studies showing a negative association between caffeine intake and bone mass may be explained by an inverse relationship between consumption of milk and consumption of caffeine-containing beverages, concluding that there is no evidence that caffeine has any harmful effect on bone status or

calcium economy in individuals ingesting recommended levels of calcium.

To date, the evidence indicates that the significance of caffeine's potential to affect calcium balance and bone metabolism adversely is dependent on lifetime caffeine and calcium intakes and is biologically more relevant in women. Current data suggest that caffeine intakes of  $<400 \text{ mg day}^{-1}$  do not have significant effects on bone status or calcium balance in individuals ingesting at least  $800 \text{ mg calcium day}^{-1}$  (an intake that  $<50\%$  of Canadian women achieve).

## Effects on human behaviour

### *Mood and performance in adults*

The results of studies on the effects of caffeine on various psychomotor tasks (reviewed by James 1991e, Smith 1998) are sometimes conflicting. For example, some studies have shown no effects of caffeine on hand steadiness, whereas others have associated caffeine consumption with poorer performance in this parameter (Bovim *et al.* 1995). Studies showing both positive effects (Jacobson and Edgley 1987, Roache and Griffiths 1987) and no effects (Zahn and Rapoport 1987) on reaction time have also been reported.

Inconsistent results can be encountered in the literature in terms of the impact of caffeine on cognitive functioning, including alertness, vigilance, memory and mood. These inconsistencies may be due to methodological differences, personality differences (e.g. introverts versus extroverts), the time of day when tests were conducted, and uncontrolled confounding factors (e.g. habitual caffeine, alcohol or tobacco use) (James 1991e, Smith 1998). In general, caffeine ( $100 \text{ mg day}^{-1}$  for 4 days, Leathwood and Pollet 1982/83;  $1.5\text{--}3 \text{ mg kg}^{-1}$  bw as single doses, 2 h apart, or  $105\text{--}210 \text{ mg}$  for a 70-kg adult, Smith *et al.* 1993;  $250 \text{ mg day}^{-1}$  for 2 days, Johnson *et al.* 1990; two doses of 200 mg, Regina *et al.* 1974) has been shown to increase the alertness of individuals, especially in situations where arousal is low (e.g. night-shift workers, early in the morning). Caffeine can also increase vigilance in the daytime. In a double-blind placebo-controlled study in males, statistically significant increases were observed in two of three vigilance tests, including both visual and auditory tests, at all

caffeine doses employed (as low as 32 mg caffeine up to 256 mg) (Lieberman *et al.* 1987). In another investigation of the effects of caffeine on alertness, subjects given caffeine (250 mg twice per day) performed significantly better in an auditory vigilance test than did the placebo group (Zwyghuizen-Doorenbos *et al.* 1990).

Most studies on the effects of caffeine on psychomotor and cognitive parameters deal with acute administration. In a study on regular consumers of coffee and tea (Jarvis 1993), higher levels of coffee consumption were associated with improved performance in reaction time, verbal memory and visuospatial reasoning. The consumption of tea was related to an improved performance in one test of reaction time and in visuospatial reasoning, but not in the other tests. The best performance was noted at an intake of five to six cups of coffee or tea per day.

Although the results of studies on the effects of caffeine on alertness, vigilance and memory are sometimes contradictory in terms of whether caffeine produces beneficial effects or no effects, there is little indication that intake of caffeine (up to approximately 250 mg in a single dose or over a few days) affects these processes in a negative manner (Smith 1998). However, a single caffeine dose of 100 mg was shown to affect short-term memory adversely in one study (Terry and Phifer 1986).

Some studies have noted little or no change in mood after the consumption of single doses of caffeine of 32 mg (Lieberman *et al.* 1987), 100 mg (Svensson *et al.* 1980) or 200 mg (Swift and Tiplady 1988). Larger amounts of caffeine (200, 400 or 600 mg as a single dose) have been associated not only with slight increases on an anger/hostility scale, but also with reduced ratings for drowsiness and incoordination (Roache and Griffiths 1987). Caffeine has little effect in producing depression, even at the consumption of more than eight cups of coffee per day (James 1991f). It is unclear why some studies have found effects on mood and others have not.

The consumption of caffeine by adults has been associated with an increase in anxiety in several studies. Many studies conducted on psychiatric inpatients, for example, have shown significantly increased anxiety levels in heavier users of caffeine (James 1991f); however, some of these studies did not control for alcohol and tobacco use, and patients may have been primed to report more symptoms. James *et al.* (1987) remedied these methodological

problems in a survey of 173 psychiatric in-patients, reporting no association between the consumption of caffeine and anxiety. In patients with generalized anxiety disorder, the administration of caffeine increased their already high anxiety level in a dose-related manner (Bruce *et al.* 1992). Note that the results of studies using psychiatric patients or patients with anxiety disorders may not be applicable to the general population (James and Crosbie 1987). Other studies have shown no effects of caffeine (e.g. regular consumption of up to seven or more cups of coffee or tea per day) on anxiety in psychiatric patients, non-clinical subjects or patients with anxiety disorders (Lynn 1973, Hire 1978, Eaton and McLeod 1984, Mathew and Wilson 1990, James 1991f, Smith 1998).

The literature suggests that caffeine can produce anxiety or exacerbate anxiety in adults with pre-existing anxiety disorders; however, the doses associated with these effects are large (1–2 g caffeine day<sup>-1</sup>) and would likely be consumed only by a small segment of caffeine consumers. In addition, it has been suggested that people experiencing the anxiogenic effects of caffeine are likely to avoid the use of this substance (James 1991f); thus, the self-limiting nature of caffeine intake would reduce any potential that caffeine had to produce anxiety in adults.

Studies have shown that caffeine can increase the time taken to fall asleep (sleep latency) and reduce sleep duration, especially if large amounts of caffeine (>3 mg kg<sup>-1</sup> bw, >210 mg for a 70-kg person) are ingested close to the usual bedtime of the individual (Smith 1998). High consumers of caffeine are less likely to report sleep disturbances than individuals consuming caffeine more infrequently (Snyder and Sklar 1984, Zwyghuizen-Doorenbos *et al.* 1990), suggesting the development of tolerance to the effects of caffeine on this parameter. It is apparent that if caffeine ingestion (especially in the late evening) affects the sleep of the individual, a self-limiting reduction in caffeine intake will likely occur to avoid any effects on sleep.

In summary, the moderate consumption of caffeine in normal adults has not been associated with any major adverse effects on mood or performance, and most effects associated with higher consumption rates would be self-limiting. However, in light of inconsistent results in the literature and individual differences in sensitivity to caffeine, some people (e.g. those with anxiety disorders) need to be aware of the possible adverse effects of caffeine and to limit their intake accordingly.

### *Tolerance, physical dependence, and withdrawal*

The literature on the development of tolerance to the effects of caffeine during prolonged ingestion is sparse and inconsistent (James 1991e). Any tolerance that may be present is likely to be dependent on the biological or behavioural effect produced by caffeine and by the level and pattern of caffeine consumption.

Cessation of caffeine ingestion has been associated with a wide variety of mainly subjective effects, in particular headache (Rubin and Smith 1999) and fatigue, characterized by such symptoms as mental depression, weakness, lethargy, apathy, sleepiness and decreased alertness (Griffiths and Woodson 1988). The general caffeine withdrawal pattern appears to be an onset from 12 to 24 h after cessation, a peak at 20–48 h, and a duration of about 1 week (Griffiths and Woodson 1988). The strength of the association between caffeine cessation and withdrawal is supported by the fact that symptoms can be ameliorated by administration of caffeine tablets in a dose-dependent manner (Griffiths and Woodson 1988). The intensity of the symptoms has been described as mild to extreme. The presence or absence of withdrawal symptoms is not always predictable, as some heavy users have ceased ingestion of caffeine with no apparent withdrawal (Griffiths and Woodson 1988).

Symptoms associated with caffeine withdrawal have been noted in studies involving the cessation of regular consumption of high ( $\leq 1250$  mg day<sup>-1</sup>, Griffiths *et al.* 1986;  $\leq 2548$  mg day<sup>-1</sup>, Strain *et al.* 1994) and much lower doses (100 mg day<sup>-1</sup>, Griffiths *et al.* 1990; 235 mg day<sup>-1</sup>, Silverman *et al.* 1992; 290 mg day<sup>-1</sup>, Weber *et al.* 1993; 428 mg day<sup>-1</sup>, Bruce *et al.* 1991; four to six cups of coffee per day, van Dusseldorp and Katan 1990; five cups of coffee per day, Hughes *et al.* 1991). While some studies have shown a dose-dependent increase in the effects of withdrawal (increased headaches after the stoppage of regular consumption of >700 mg caffeine day<sup>-1</sup> compared with  $\leq 700$  mg day<sup>-1</sup>; Weber *et al.* 1993), others have shown little correlation between daily intake and withdrawal symptoms (in a range of regular intake of 231–2548 mg day<sup>-1</sup>; Strain *et al.* 1994). In Strain *et al.* (1994), the most severe effects upon cessation were noted with the lowest consumption, while the individual with the highest regular consumption reported only moderate effects.

Dews *et al.* (1998) hypothesized that bias and priming of the subjects in caffeine withdrawal studies led to

the exaggeration of the incidence and severity of symptoms of caffeine withdrawal. They suggested that the prevalence and severity of withdrawal symptoms have been exaggerated in the literature, as illustrated by the variability among published reports of both the symptoms associated with caffeine withdrawal and the incidence rates, and concluded that the true level of caffeine withdrawal is low and near background levels. Also, there are reports of caffeine withdrawal continuing for long periods, which may be the result of a return of performance and alertness to pre-caffeine conditions. Since caffeine has been shown to improve these parameters, the return to normalcy may be associated with reduced performance and alertness compared with caffeine use, and these effects may be attributed to a caffeine withdrawal syndrome or as a sign that physical dependence has been produced during caffeine consumption.

In a blinded study by Dews *et al.* (1999), subjects were given coffee and then subjected to continued caffeine intake, abrupt caffeine cessation or gradual caffeine cessation (from 100 to 0% over 7 days). Subjects in the gradual cessation group reported no adverse effects of caffeine cessation, while females (but not males) in the abrupt cessation group had adverse effects, as evidenced by reduced mood/attitude scores on no-caffeine days (reductions in scores were small). This study showed that the blinding of subjects to caffeine cessation reduced the incidence of reported symptoms of caffeine withdrawal, as about half of the subjects reporting severe withdrawal symptoms in a prior telephone interview experienced no symptoms of withdrawal in the blinded study.

The literature thus supports the existence of caffeine withdrawal in some individuals, with variability in the severity of symptoms. When withdrawal occurs, it is short-lived and relatively mild in the majority of people affected.

### *Effects on children*

Scientific studies have shown a variety of effects of caffeine consumption in children, although it is surprising that so few studies have specifically addressed effects in this population.

At low doses, an increased performance in attention tests has been noted in children. A double-blind and

placebo-controlled study was conducted in which 21 children (mean body weight  $38.1 \pm 12.5$  kg; average age  $10.6 \pm 1.3$  years) were administered a placebo, a low dose of caffeine (single dose of  $2.5 \text{ mg kg}^{-1}$  bw) or a high dose of caffeine (single dose of  $5.0 \text{ mg kg}^{-1}$  bw) (Bernstein *et al.* 1994). The authors noted a statistically significant, dose-dependent improvement in a performance test of attention after caffeine administration compared with the placebo group. A significant but non-dose-related improvement in a manual dexterity test was also noted. In a double-blind placebo-controlled cross-over study (Elkins *et al.* 1981, Rapoport *et al.* 1981b), a group of 19 pre-adolescent boys were tested for a number of parameters after the ingestion of a placebo or a single caffeine dose of 3 or  $10 \text{ mg kg}^{-1}$  bw on three separate occasions (each separated by 48 h). The children in the high-dose group showed a significant increase in motor activity compared with the control and low-dose groups, an increase in speech rate compared with the low-dose group, a significant reduction in reaction time in a vigilance test, and a reduced number of errors in a sustained attention measure test compared with the placebo group. Stratification of usual, pre-study caffeine use was not conducted for the subjects in this study.

Anxiety, measured both subjectively and objectively, has also been associated with the administration of low doses of caffeine in children in a number of studies. In the Bernstein *et al.* (1994) study described above, there was a trend (although it was statistically non-significant) towards a higher level of anxiety in one of the subsets of the Visual Analogue Scale for state anxiety ('how I feel right now') just after caffeine administration. There was a statistically significant correlation between salivary caffeine concentration and the severity of the state anxiety as measured by the Visual Analogue Scale. It was noted in this study that the levels of salivary caffeine were significantly correlated with the dose of caffeine administered. Other anxiety measurements conducted in this study (all self-reported, including other measurements of state and trait anxiety) showed no difference after caffeine administration. While this study randomized the order of testing, there was a lack of participant stratification based on regular, pre-study caffeine consumption. Even so, the level of caffeine administered to children in the Bernstein *et al.* (1994) study is the lowest in the available literature, and this study should be considered along with the wider body of evidence.



Other reviewed studies showing manifestations of anxiety in children associated with caffeine were those by Rapoport *et al.* (1981a) ( $10 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ), Rapoport *et al.* (1981b) ( $3$  and  $10 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ) and Rapoport *et al.* (1984) ( $10 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ). In all of these studies, effects on anxiety were noted at all doses tested. Other effects in these studies included being nervous, fidgety, jittery, and restless and experiencing hyperactivity and difficulty sleeping. Positive dose-responses were noted for skin conductance (a measure of anxiety) as well as for nervous/jittery behaviour in the children in the Rapoport *et al.* (1981b) study. When subjects were stratified by pre-study caffeine intake (Rapoport *et al.* 1981a), differences between low and high dose consumers (pre-study intake of  $<50$  and  $\geq 300 \text{ mg caffeine day}^{-1}$ , respectively) were apparent. High dose consumers were more easily frustrated, with a greater feeling of nervousness on baseline tests, than the low consumer group, possibly pointing to caffeine withdrawal during this period of testing. In terms of reported side-effects, the low users could distinguish between the placebo and the caffeine treatment (according to a variety of self-reported side-effects), while the high users could not. The high users given placebo and then caffeine experienced more side-effects during the initial placebo administration than they did when administered caffeine. The study by Rapoport *et al.* (1981a) appears to provide evidence of tolerance in the high regular consumers, and this group also appeared to show withdrawal in the baseline and placebo conditions. In Rapoport *et al.* (1984), a number of differences were noted between high and low consumers in terms of behaviour. During the screening, baseline and initial pre-study caffeine-free periods, the high consumers reported significantly more symptoms of anxiety and were reported to be more 'disobedient' than the low consumers. There appeared to be many differences between the groups when caffeine was administered for 2 weeks. Low consumers exhibited a significant increase in restlessness and fidgety behaviour, while the high-dose group showed a decrease in this behaviour. Statistically significant differences between the groups were mood changes, excitability, inattentiveness, restlessness and crying (the direction of these changes between the two groups was not mentioned in the paper). In terms of side-effects during this period, the low consumers reported headache, stomach-ache and nausea. These effects were not noted in the high consumers. A feeling of faintness and of being flushed was significantly increased in the low consumers and signifi-

cantly decreased in the high consumers. Also, the low consumers had difficulty sleeping and a decreased appetite compared with the high consumer group. It was suggested by the authors that child consumers of high-caffeine diets differ inherently from those consuming low-caffeine diets in certain ways, namely having lower autonomic arousal and being more impulsive, leading to the self-administration of caffeine. In this study the initial pre-study stratification of subjects into high and low consumers ( $18 \pm 18$  and  $641 \pm 350 \text{ mg day}^{-1}$ , respectively) was based on a 24-h recall; however, based on a 7-day food diary for the pre-study baseline period, it was observed that there was a large overlap between the low and high consumer groups ( $95 \pm 84$  and  $290 \pm 275 \text{ mg week}^{-1}$  or about  $41.4$  and  $13.6 \text{ mg day}^{-1}$ , respectively). The overlap in pre-study caffeine intake may reduce the ability to evaluate the differential effects of caffeine on high and low consumers that were noted.

Other studies dealing with the effects of caffeine on children were those by Baer (1987), Hale *et al.* (1995) and Davis and Osorio (1998). The study by Baer (1987) used six 5-year-old children who were administered either a caffeine-free or a caffeinated soft drink each day for 2 weeks, resulting in a dose of  $1.6\text{--}2.5 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  when caffeine was administered. Drink conditions were reversed at the end of the 2 weeks. Effects noted on behaviour (e.g. off-task behaviour, motor activity, continuous performance) were inconsistent and small. No testing for anxiety was conducted. Hale *et al.* (1995) examined the self-administration of caffeine in 18 adolescent children of both sexes (age 11–15) in a double-blind, placebo-controlled study. Soft drinks containing either caffeine ( $33.3 \text{ mg}/8$  ounce serving) or a placebo were supplied to the participants. The children consumed a particular drink one day (either caffeinated or placebo) followed by another drink (either the same as the previous day or different) the next day. Consumption of all drinks was *ad libitum*. Four children met the criteria for repeatable self-administration, preferring the caffeinated drink to the placebo; however, only one child had a statistically significant self-administration. In these four children, the average intake of caffeine was  $169 \text{ mg day}^{-1}$  compared with  $62 \text{ mg day}^{-1}$  in those where self-administration was not evident. No behavioural symptoms were consistently reported in any participant. When the results were analysed across all participants, it was noted that on caffeine-free beverage days, there was significantly more depression, drowsiness and fatigue. No differences between the consumption of caffeinated

nated or non-caffeinated drinks were observed in the children when a parent rating scale for anxiety, hyperactivity or impulsivity was employed. No information was provided in this study about the pre-study intake of caffeine. Davis and Osorio (1998) reported that caffeine intake can worsen and trigger the appearance of tics in children, based on two children aged 11 and 13. The authors concluded that consumption of caffeine can trigger the appearance of tics in susceptible children, although they made no indication of how the determination of a 'susceptible' child could be made. It is possible that genetic factors play a role, since the two children in this study were related. It should be recognized that with only two children, this study is only suggestive of a problem; however, it is an area that deserves further research.

In a meta-analysis of nine studies (Stein *et al.* 1996), caffeine showed no significant deleterious acute effects on behaviour or cognition in children. The results of the meta-analysis with respect to anxiogenic effects are difficult to interpret, for several reasons. For example, tests of anxiety were grouped with a number of other tests to form an 'internalizing' category. This may have diluted any effects of anxiety. In addition, the tests used to assess anxiety were not the same in each study, making comparisons between these studies more difficult. Of the nine studies used for the meta-analysis, four dealt with normal children, while the remainder used children who had attention deficit hyperactivity disorder. Again, this makes the inter-comparison of studies difficult.

The cessation of caffeine intake in normally high consuming children ( $\geq 300 \text{ mg day}^{-1}$ ) or those administered larger amounts of caffeine ( $10 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ) over a period of weeks has resulted in the production of symptoms associated with caffeine withdrawal (Rapoport *et al.* 1981a). Bernstein *et al.* (1998) studied the single-blinded withdrawal of caffeine in 30 normal pre-pubertal children (mean age 10 years) having an average pre-study consumption of at least  $20 \text{ mg caffeine day}^{-1}$ . Children were administered  $150 \text{ mg caffeine day}^{-1}$  for 13 days followed by a non-caffeinated drink for 1 day, then resumed their normal diet. While on caffeine, the subjects responded significantly faster in the test of attention than in the withdrawal period and resumption to normal diet period. During the withdrawal period, the response time was significantly increased compared with the pre-caffeine (baseline) period. This increased response time was still significantly elevated 1 week post-caffeine cessation. The authors suggested that the

children had developed a physical dependence on the caffeine and exhibited withdrawal effects upon removal of the caffeine. Anxiety was observed to be higher during the baseline period in this study, with scores decreasing over time, possibly related to an increasing familiarity of the children with the testing procedure.

Caffeine has been tested for use in the treatment of hyperactivity/attention deficit disorder in children (James 1991e, Leviton 1992). A few early studies showed beneficial effects of caffeine intake at doses ranging from  $175$  to  $600 \text{ mg day}^{-1}$ ; in these studies, few adverse effects were noted, although some effect on sleep (dose-dependent insomnia) was noted in one study ( $100\text{--}400 \text{ mg caffeine day}^{-1}$ ), and minor group increases in blood pressure and heart rate were noted in another ( $300 \text{ mg day}^{-1}$ ). Many other studies, however, have shown no benefit of caffeine use in children with attention deficit disorder. Some studies, in fact, suggest that caffeine ingestion can lead to symptoms of hyperactivity in natural low consumers. In a study in which the 7-day food diaries from 30 low- and 30 high-caffeine-consuming school children were analysed, 30% of the high consumers met criteria for attention deficit disorder with hyperactivity, and the high consumers were perceived as being more restless than the low consumers (Rapoport *et al.* 1984). Problems with this study in terms of overlap between the low and high consumers' pre-study intake of caffeine have been noted above.

The studies reviewed here and their sometimes conflicting results can be difficult to compare, since they employed either different endpoints or different ways to assess similar endpoints. In addition, most studies used a small number of subjects. The problems associated with differing groups of caffeine consumers within the population of children and the potential differential susceptibility to caffeine of certain sub-populations need to be clarified. Another difficulty with some studies is the non-stratification of children based on their usual (pre-study) caffeine intake, since high consumers and low consumers may not always respond in the same manner to additional administered caffeine. In addition, no studies have been designed to test for potential chronic effects of caffeine consumption by children.

In conclusion, it is unknown if long-term daily consumption of caffeine would produce effects similar to those observed in the studies reviewed above. However, it is known that the human nervous system (including the brain) continues to develop and mature

throughout childhood. It is possible that the protracted development of the nervous system may render children more sensitive to any adverse effects of caffeine.

### Mutagenicity/genotoxicity

Caffeine not only induces mutations in bacteria in the absence of mammalian metabolic activation, but also can exhibit weak antimutagenic activity in some microorganisms (Legator and Zimmering 1979, Brusick *et al.* 1986, Rosenkranz and Ennever 1987, Pons and Muller 1990). In eukaryotic organisms, including fungi and yeasts (Legator and Zimmering 1979, Osman and McCready 1998), higher plants (Gonzalez-Fernandez *et al.* 1985, Manandhar *et al.* 1996), rodent cell lines (Jenssen and Ramel 1980, Aeschbacher *et al.* 1986, Brusick *et al.* 1986, Haynes *et al.* 1996, Kiefer and Wiebel 1998), and human cell lines (Lachance 1982, Bernhard *et al.* 1996, Roldan-Reyes *et al.* 1997), caffeine inhibits cell cycle-dependent DNA repair induced by a variety of physical and chemical mutagens, leading to the potentiation of clastogenic effects (D'Ambrosio 1994, Puck *et al.* 1998, Harish *et al.* 2000, Jiang *et al.* 2000). In chick embryo cells, DNA damage was induced (Müller *et al.* 1996) at dose levels in the  $\geq 1$  mM range, not considered toxicologically relevant (Tempel and von Zallinger 1997). Genotoxic activity in *Drosophila* was weakly positive or inconclusive for chromosomal effects, dominant lethals, the somatic mutation and recombination test, and chromatid aberrations (Legator and Zimmering 1979, Graf and Würzler 1986, 1996), while X-ray damage was enhanced (De Marco and Cozzi 1980). Only at high levels of caffeine were clastogenic effects reported in somatic cells of rodents (Jenssen and Ramel 1980, Aeschbacher *et al.* 1986, Haynes *et al.* 1996), while no specific locus mutations or chromosomal effects were induced in germ cells or embryonic cells (Legator and Zimmering 1979, Mailhes *et al.* 1996, Müller *et al.* 1996). Antigenotoxic activity on somatic or germ cells exposed to a variety of physical and chemical mutagens, following ingestion of caffeinated or decaffeinated coffees was weak or negative (Legator and Zimmering 1979, Everson *et al.* 1988, Reidy *et al.* 1988, Chen *et al.* 1989, MacGregor 1990, Smith *et al.* 1990, Robbins *et al.* 1997, Vine *et al.* 1997, Abraham and Singh 1999).

Although evidence for the mutagenic potential of caffeine is conflicting (Lachance 1982, Grice 1987, Rosenkranz and Ennever 1987, D'Ambrosio 1994), it appears to be unlikely that at normal, physiologically relevant levels of consumption (i.e. at less than systemic toxicity ranges), caffeine would result in mutagenic effects in humans.

### Carcinogenicity

The evidence from several oral oncogenicity/chronic toxicity studies in mice (Bauer *et al.* 1977, Macklin and Szot 1980, Stalder *et al.* 1990) and rats (Wurzner *et al.* 1977, Johansson 1981, Takayama and Kuwabara 1982, Mohr *et al.* 1984) indicate that caffeine is not a carcinogen, up to dose levels of 391 and 230 mg kg<sup>-1</sup> bw day<sup>-1</sup>, respectively. The most common clinical sign observed in these studies was a decrease in body weight, with no concomitant decrease in food consumption.

Epidemiological studies on the carcinogenicity of caffeine as present in coffee have consistently shown that caffeine is not associated with cancer development at several tissue and organ sites. For example, caffeine consumption, from three or more cups of coffee per day ( $\geq 300$  mg caffeine day<sup>-1</sup>) was not associated with cancer development in the following sites: large bowel in 13 case-control studies (cited in IARC 1991a, Lee *et al.* 1993, Olsen and Kronborg 1993); stomach in six case-control studies (cited in IARC 1991a, Agudo *et al.* 1992); prostate in one case-control study (cited in IARC 1991a); liver in one case-control study (cited in IARC 1991a); lung in two cohort studies and one case-control study (cited in IARC 1991a); and vulva in one case-control study (Sturgeon *et al.* 1991). Higher caffeine consumption, specifically drinking seven or more cups of coffee per day ( $\geq 700$  mg caffeine day<sup>-1</sup>) was not associated with breast cancer in 11 case-control studies (cited in Rohan *et al.* 1989, IARC 1991a, McLaughlin *et al.* 1992, Folsom *et al.* 1993, Smith *et al.* 1994, Tavani *et al.* 1998).

On the other hand, caffeine intake, as measured by coffee consumption, was occasionally associated with cancer development at some sites. In the urinary bladder, four cohort studies showed no effect with doses of five or more cups of coffee per day ( $\geq 500$  mg caffeine day<sup>-1</sup>) (cited in IARC 1991a, Chyou *et al.*

1993, Stensvold and Jacobsen 1994). In 26 case-control studies, 17 studies showed no effect with doses of five or more cups of coffee per day. Nine studies were positive, and three of these studies showed a dose-response (cited in IARC 1991a, Vena *et al.* 1993, Donato *et al.* 1997). Of these three studies, two showed a positive increase with any coffee consumption, and the third study was significant only when consumption was five or more cups of coffee per day. In the pancreas, out of nine cohort studies, eight showed no significant effect with doses of five or more cups of coffee per day ( $\geq 500$  mg caffeine day<sup>-1</sup>), while one study was positive for any coffee consumption (cited in IARC 1991a, Stensvold and Jacobsen 1994, Harnack *et al.* 1997). Of 24 case-control studies, 21 showed no effect on pancreas with doses of five or more cups per day. In one of the three positive case-control studies, a significant effect was observed only when four cups of coffee per day were drunk (400 mg caffeine day<sup>-1</sup>). In a second study, doses exceeding two cups of coffee per day (200 mg caffeine day<sup>-1</sup>) were associated with an increase. In the third positive study, any level of coffee drinking resulted in an increased risk. Of the three positive studies, two studies showed a dose-related response. When smoking was taken into consideration, the positive responses in these studies were weakened (cited in IARC 1991a, Bueno de Mesquita *et al.* 1992, Lyon *et al.* 1992, Partanen *et al.* 1995, Nishi *et al.* 1996). In the ovary, two case-control studies showed a significant increase in cancer incidence with doses of more than one cup of coffee per day, while five case-control studies showed no effect with doses of five or more cups per day (cited in IARC 1991b, Polychronopoulou *et al.* 1993). In the skin, a case-control study showed that the risk of basal cell carcinoma was increased with doses of more than two-and-a-half cups of coffee per day ( $>250$  mg caffeine day<sup>-1</sup>) (Sahl *et al.* 1995).

Overall, the evidence indicates that caffeine, as present in coffee, is not a chemical that causes breast or bowel cancer. Results on the association between caffeine and the development of urinary bladder and pancreatic cancer are inconsistent and the data are not conclusive. At other sites (e.g. ovary, stomach, liver) the data are insufficient to conclude that caffeine consumption is related to carcinogenesis. Based on the studies reviewed in this report, caffeine is not likely to be a human carcinogen at a dose less than five cups of coffee per day ( $<500$  mg caffeine day<sup>-1</sup>).

## Reproductive and developmental effects

There is evidence that many women spontaneously reduce their caffeine intake during pregnancy, some apparently developing a temporary 'loss of taste' for the substance. Nevertheless, caffeine consumption in this group can remain relatively high. About 98% of women of reproductive age regularly consume caffeine in the form of caffeinated beverages or in caffeine-containing medications, while 72% of them continue to do so during pregnancy (James 1991g). Epidemiological investigations reviewed for this paper showed that a majority of women consumed caffeine during pregnancy in a range of 100–300 mg day<sup>-1</sup> (Fenster *et al.* 1991a, Fortier *et al.* 1993, Mills *et al.* 1993, Dominguez-Rojas *et al.* 1994, Rondo *et al.* 1996). A small proportion of pregnant women in the population may ingest a much greater amount,  $\geq 400$  mg caffeine day<sup>-1</sup> (Kurppa *et al.* 1983, Toubas *et al.* 1986, Olsen *et al.* 1991, Armstrong *et al.* 1992, McDonald *et al.* 1992a).

During the past 20 years, a great deal of evidence has accumulated concerning the effects of caffeine consumption on reproduction and pre- and postnatal development. Although the results from studies reviewed for this publication have not been entirely consistent, the bulk of evidence suggests that caffeine intake at dose levels of  $\geq 300$  mg day<sup>-1</sup> may have adverse effects on some reproductive/developmental parameters when exposure takes place during certain periods (Dlugosz and Bracken 1992).

Christian and Brent (2001) reviewed published animal and human epidemiological studies investigating the association between caffeine ingestion and adverse reproductive/developmental effects and concluded that pre-pregnant or pregnant women who do not smoke or drink alcohol and who consume moderate amounts of caffeine ( $\leq 5$ – $6$  mg kg<sup>-1</sup> bw day<sup>-1</sup> spread throughout the day) will be unlikely to develop reproductive problems.

The effects of caffeine on the outcome of pregnancy appear biologically plausible. Published data suggest that the human foetus and neonate may be exposed to substantial amounts of caffeine or its metabolites, as caffeine ingested by the mother is rapidly absorbed from the gastrointestinal tract, readily crosses the placenta and is distributed to all foetal tissues, including the central nervous system. Caffeine is also excreted in mother's milk. In addition, exposure of the foetus and newborn to caffeine is enhanced due to

the half-life of caffeine being markedly increased in the foetus (the enzymes involved in the oxidation of methylated xanthines are absent in the foetus), newborn infant and pregnant woman in comparison with non-pregnant adults and older children (James and Paull 1985, James 1991g, Dlugosz and Bracken 1992).

### *Effects on conception and female fertility*

Caffeine consumption is one of many factors implicated in the reduction of fecundity, or the capacity to reproduce. There are several plausible biological mechanisms by which caffeine could delay conception. Caffeine consumption has been associated with alteration of hormone levels (e.g. oestradiol), with tubal disease or endometriosis, with altered tubal transport time, and with reduced viability of the fertilized ovum (Alderete *et al.* 1995). Caffeine metabolism varies during the menstrual cycle, with reduced clearance during the luteal phase, resulting in greater accumulation during the period of implantation and early embryonic development. Caffeine consumption may lead to pregnancy loss, which might result in prolongation of the waiting time required to achieve a clinically recognized pregnancy (Stanton and Gray 1995).

Thirteen epidemiological studies (retrospective and prospective data collection) investigating the relationship between coffee/caffeine consumption and time to conception (fecundability) present conflicting results. Five studies reported no delay in conception in women who consumed up to  $\geq 700$  mg caffeine day<sup>-1</sup> before pregnancy. In a multicentre study conducted in the USA and Canada, caffeine consumption was not associated with decreased fertility in a group of 2817 women whose caffeine consumption from all sources ranged from 100 to  $\geq 240$  mg day<sup>-1</sup> (Joesoef *et al.* 1990). Results of a study by Olsen (1991) showed no association between subfecundity and consumption of coffee or tea at any dose level (none to eight cups per day) among non-smoking women. Florack *et al.* (1994) showed that participants (male and female partners) with caffeine intake of 400–700 mg day<sup>-1</sup> had a higher fecundability than those with a lower intake level; only heavy caffeine intake ( $>700$  mg day<sup>-1</sup>) among partners was negatively related to fecundability when compared with the lowest intake level ( $<300$  mg day<sup>-1</sup>). Caan *et al.* (1998) found no association between caffeine intake at a mean dose level of about 90 mg day<sup>-1</sup> and a reduction in fertility

of women trying to conceive for at least 3 months. Alderete *et al.* (1995) examined the independent and combined effects of smoking and coffee consumption on time to conception in 1341 primigravid women and found that women who consumed more than three cups of coffee per day ( $>300$  mg caffeine day<sup>-1</sup>) but did not smoke showed no decrease in fertility when compared with non-coffee-drinking women (adjusted odds ratio [OR] = 1.0–1.2) who did not smoke.

Results from two studies showed a significant decrease in monthly probability of pregnancy among women who consumed the equivalent of three or more cups of coffee per day ( $\geq 300$  mg caffeine day<sup>-1</sup>). In a retrospective study of 2465 women, Stanton and Gray (1995) found that the adjusted OR of delayed conception for  $>1$  year was not increased among women who consumed  $\leq 300$  mg caffeine day<sup>-1</sup>, but the OR was 2.65 (95% confidence interval [CI] = 1.38–5.07) among non-smokers who consumed  $\geq 301$  mg caffeine day<sup>-1</sup>. (In this study, no effect of high caffeine consumption was observed among women who smoked.) In a study of 430 Danish couples planning their first pregnancy, Jensen *et al.* (1998) found that compared with non-smoking couples with caffeine intake  $<300$  mg day<sup>-1</sup>, non-smoking females and males who consumed 300–700 mg caffeine day<sup>-1</sup> had fecundability ORs of 0.88 and 0.87 (95% CI = 0.60–1.31 and 0.62–1.22), respectively, whereas females and males with a higher caffeine intake ( $>700$  mg day<sup>-1</sup>) had ORs of 0.63 and 0.56 (95% CI = 0.25–1.60 and 0.31–0.89), respectively. No dose–response relationship was found among smokers. Smoking women whose only source of caffeine was coffee ( $>300$  mg day<sup>-1</sup>) had a reduced fecundability OR = 0.34 (95% CI = 0.12–0.98), and non-smoking women with a caffeine intake of  $>300$  mg day<sup>-1</sup> from other sources had a low, but non-significant, OR = 0.43 (95% CI = 0.16–1.13) compared with non-smoking women consuming  $<300$  mg caffeine day<sup>-1</sup>. The authors concluded that the results indicated a possible association between male and female caffeine intake and decreased fecundability only among non-smokers.

Another four studies reported delayed conception in women who consumed  $\geq 400$ ,  $\geq 500$ , or  $\geq 800$  mg caffeine day<sup>-1</sup>. Data collected by Christianson *et al.* (1989) showed a dose-related effect of coffee consumption on reported difficulties in becoming pregnant. Women who were heavy coffee drinkers before pregnancy (four to seven or more cups of coffee per day) experienced almost double the time in becoming

pregnant compared with women who consumed none or one cup of coffee per day. Williams *et al.* (1990) examined data from a large cross-sectional study on 3010 postpartum women, finding that times to conception for women who consumed three, two, one or no cups of coffee per day were similar (ranging from 4.8 to 5.0 months), whereas time to conception was longer (6.6 months) for the 129 women who consumed four or more cups of coffee per day (approximately 400 mg caffeine day<sup>-1</sup>). In a retrospective study by Bolumar *et al.* (1997), a significantly increased OR (1.45, 95% CI = 1.03–2.04) for subfertility in the first pregnancy was observed among women consuming >500 mg caffeine day<sup>-1</sup>. Women in this highest level of consumption had an increase of 11% in the time leading to the first pregnancy. (The effect of drinking >500 mg caffeine day<sup>-1</sup> was relatively stronger in smokers [OR = 1.56, 95% CI = 0.92–2.63] than in non-smokers [OR = 1.38, 95% CI = 0.85–2.23].) In Olsen (1991), a statistically significant association was observed (OR = 1.35, 95% CI = 1.02–1.48) for a delay of  $\geq 1$  year in women who smoked and also consumed at least eight cups of coffee per day (or an equivalent amount of caffeine from 16 cups of tea).

Three studies found modest positive associations with delayed conception from maternal consumption of more than one caffeinated beverage per day. A prospective study by Wilcox *et al.* (1988) showed that women who consumed more than one cup of coffee per day (126 mg caffeine day<sup>-1</sup>) were half as likely to conceive during a given menstrual cycle. In a cross-sectional study, Hatch and Bracken (1993) found that intake of caffeine from coffee, tea and caffeinated soft drinks was associated with an increased risk of a delay of conception of  $\geq 1$  year. Compared with no caffeine use, consumption of 1–150 mg caffeine day<sup>-1</sup> resulted in an OR for delayed conception of 1.39 (95% CI = 0.90–2.13), consumption of 151–300 mg day<sup>-1</sup> was associated with an OR = 1.88 (95% CI = 1.13–3.11), and consumption of >300 mg day<sup>-1</sup> resulted in an OR = 2.24 (95% CI = 1.06–4.73). Women who reported drinking >300 mg caffeine day<sup>-1</sup> had a 27% lower chance of conceiving for each cycle, and those who reported drinking <300 mg day<sup>-1</sup> had a 10% reduction in conception rates per cycle compared with women who consumed no caffeine. Hakim *et al.* (1998) examined the effects of caffeine consumption on conception in a prospective study of 124 women, finding that the consumption of the equivalent of more than one cup of coffee per day among the sample of

women who neither smoked nor drank alcohol was associated with a decreased risk of conception (18.0%, adjusted OR = 0.56, 95% CI = 0.23–1.33), which did not reach statistical significance.

In one of the above-described studies, delayed conception was observed among non-smoking women who consumed >300 mg caffeine day<sup>-1</sup>, but not among women who smoked (Stanton and Gray 1995). Also, Jensen *et al.* (1998) found no dose-response relationship among smokers at caffeine doses of up to  $\geq 700$  mg day<sup>-1</sup>, whereas non-smoking males and females who consumed 300–700 mg day<sup>-1</sup> exhibited decreased fecundability compared with non-smoking couples with caffeine intake of <300 mg day<sup>-1</sup>. However, in Olsen (1991), no association was found among non-smokers at any dose level of caffeine, just for women who smoked and also consumed at least eight cups of coffee per day. Bolumar *et al.* (1997) also found that the effect of drinking >500 mg caffeine day<sup>-1</sup> was relatively stronger in smokers than in non-smokers. An interaction between caffeine and smoking is biologically plausible. Reports in the literature have shown that cigarette smoking significantly increases the rate of caffeine metabolism (see 'Pharmacokinetics'). The enhanced caffeine metabolism in smokers also accelerates caffeine clearance and, as a result, reduces the duration and magnitude of the exposure.

Most epidemiological studies reviewed here were affected by methodological issues, including inadequate measurement of caffeine intake, failure to distinguish among different types of preparation and different strengths of coffee, inadequate control for possible confounding effects, recall bias in retrospective studies, lack of data on frequency of unprotected intercourse, and, in some studies, inadequate sample size. Despite these limitations, epidemiological studies are an important source of information on potential adverse effects of caffeine on fertility (delayed conception) in humans.

The evaluated epidemiological studies generally indicate that consumption of caffeine at dose levels of >300 mg day<sup>-1</sup> may reduce fecundability in fertile women.

### *Effects on sperm and male fertility*

Although ingested caffeine is capable of crossing the blood–testis barrier, caffeine consumption as a factor

that could alter male reproductive function has not been investigated extensively. Data from *in vitro* studies suggest that caffeine has variable, dose-related effects on human sperm motility, number and structure (Dlugosz and Bracken 1992). It has been reported that women undergoing artificial insemination were twice as likely to become pregnant if their husbands' semen had been treated with caffeine than if it had not. Scanning electron microscopic examination of fresh semen showed no morphological changes caused by *in vitro* treatment with caffeine (IARC 1991b, Dlugosz and Bracken 1992).

In an investigation of semen quality and its association with coffee drinking, cigarette smoking and alcohol consumption in 445 men attending an infertility clinic, coffee drinking was correlated with increases in sperm density and percentage of abnormal forms, but not in a dose-dependent manner. Men who drank one to two cups of coffee per day had increased sperm motility and density compared with subjects who drank no coffee. However, men who drank more than two cups per day had decreased sperm motility and density. The combination of drinking more than four cups of coffee per day ( $>400$  mg caffeine  $\text{day}^{-1}$ ) and smoking  $>20$  cigarettes per day diminished spermatozoan motility and increased the percentage of dead spermatozoa. No alteration in the fertility of individuals who consumed these substances was observed (Marshburn *et al.* 1989, IARC 1991b, Dlugosz and Bracken 1992).

Jensen *et al.* (1998) found no association between caffeine intake and semen quality in men exposed to caffeine for an extended period at dose levels as high as  $\geq 700$  mg  $\text{day}^{-1}$ .

Based on the limited data, it is concluded that caffeine consumption at dose levels of  $>400$  mg  $\text{day}^{-1}$  may decrease sperm motility and/or increase the percentage of dead spermatozoa (only in heavy smokers), but will be unlikely to adversely affect male fertility in general.

### *Spontaneous abortion (miscarriage)*

The influence of caffeine on the risk of spontaneous abortion in humans is difficult to assess. A number of studies have been conducted that show either a positive effect or a lack of effect of caffeine on this pregnancy outcome. Shortcomings in the literature include small sample size and inadequate adjustment

for potential confounders. A major potential confounder is the presence of nausea in the first trimester of pregnancy, as a lack of nausea early in pregnancy has been associated with a significantly increased risk of miscarriage (Stein and Susser 1991). Nausea in pregnancy may cause a reduction in the consumption of coffee/caffeine, while a lack of nausea may lead to continued ingestion. This may result in an erroneous association of caffeine intake with increased risk of spontaneous abortion. Another drawback is the general lack of accurate measurement of actual caffeine consumption by the participants in the epidemiological studies. Stavric *et al.* (1988), for example, found a marked variation in caffeine content of coffee and tea depending on the method of preparation and brand, and errors also arise from differences in the size of the serving 'cup' used by different participants. Another serious limitation is the potential for poor identification of foetal loss due to enrolment of women later in the pregnancy or only those who presented to hospitals, as many early foetal losses go unnoticed by women. Studies measuring human chorionic gonadotrophin levels, such as those of Wilcox *et al.* (1990), Mills *et al.* (1993) and Hakim *et al.* (1993), should reduce any bias in this factor. In addition, the majority of the studies showing positive associations between caffeine and spontaneous abortion are retrospective in nature, and at least one study depended on information recalled after several pregnancies (Armstrong *et al.* 1992).

Most of the studies have shown no association between a caffeine intake of  $<300$  mg  $\text{day}^{-1}$  and an increased risk of spontaneous abortion (Watkinson and Fried 1985, Wilcox *et al.* 1990, Armstrong *et al.* 1992, Mills *et al.* 1993, Dlugosz *et al.* 1996, Wen *et al.* 2001). In the one study that accurately assessed caffeine intake (the prospective study by Watkinson and Fried 1985), 284 mothers were interviewed about their caffeine intake from coffee, tea, caffeinated soft drinks, chocolate bars, chocolate drinks and caffeine-containing medicines 3 years before pregnancy, during each trimester of pregnancy and the year after pregnancy. Caffeine consumption was measured and categorized into  $<100$ , 100–300 and  $>300$  mg  $\text{day}^{-1}$ . There was no association between caffeine consumption and risk of miscarriage. In this study, there was a long period for which the women had to recall their caffeine consumption, so all recalled intakes may not have been accurate. Another study that found no association between caffeine consumption at levels of  $\geq 300$  mg  $\text{day}^{-1}$  and an increase in spontaneous

abortion was the prospective study by Mills *et al.* (1993).

The meta-analysis conducted by Fernandes *et al.* (1998), using data from six original epidemiological studies (including 42 988 pregnancies), showed a positive association (small but statistically significant) of spontaneous abortion with the consumption of  $>150$  mg caffeine day<sup>-1</sup> (OR = 1.36, 95% CI = 1.29–1.45). No other more definitive consumption categories were used in this study, and adjusting for confounders was not possible. The authors described the increased risk as small and noted that 'a possible contribution to these results of maternal age, smoking, ethanol use or other confounders could not be excluded'.

Srisuphan and Bracken (1986) conducted a prospective cohort study with 3135 pregnant women whose caffeine consumption was estimated from their reported consumption of coffee, tea, caffeinated soft drinks and caffeine-containing drugs. In terms of a crude association, the rate of spontaneous abortion was 1.8% for those who did not use caffeine ( $<1$  mg day<sup>-1</sup>), 1.8% for the light users (1–150 mg day<sup>-1</sup>) and 3.1% for the moderate/heavy users ( $\geq 151$  mg day<sup>-1</sup>). When exposure was divided into 50-mg increments, there was a 'marked increase' in the relative risk for spontaneous abortion at use levels of  $>150$  mg day<sup>-1</sup>, but no dose–response was noted, as no further risk was associated with exposures  $>200$  mg caffeine day<sup>-1</sup>. This study also pointed out that coffee consumption rather than caffeine consumption *per se* may have contributed to the risk of spontaneous abortion, as those who had a caffeine consumption from coffee alone had an increased crude relative risk compared with those consuming tea or caffeinated soft drinks alone, although the differences were not statistically significant. In this study, there was no more definitive categorization of intake  $>150$  mg day<sup>-1</sup>.

Al-Ansary and Babay (1994) conducted a retrospective case-control study with 226 women in Saudi Arabia and found an increased risk of miscarriage with the consumption of  $>150$  mg caffeine day<sup>-1</sup> (OR = 1.0 [referent] and OR = 1.9 [95% CI = 1.2–3.0] for consumption of 1–150 and  $>150$  mg day<sup>-1</sup>, respectively). No subclassification of intake  $>150$  mg day<sup>-1</sup> was conducted in this study, and it appears that no confounders were taken into consideration in the analysis. Only cases that had presented to a hospital were included, which may not give a complete picture of all possible miscarriages.

The retrospective case-control study by Infante-Rivard *et al.* (1993) is one of the better papers of those showing an association between lower levels of caffeine consumption and the risk of spontaneous abortion. In total, there were 331 cases and 993 controls. The investigators found significant increases in OR for the risk of foetal loss in high consumers of caffeine when it was ingested before and during pregnancy ( $>321$  mg caffeine day<sup>-1</sup> before pregnancy, OR = 1.85, 95% CI = 1.18–2.89; 163–321 and  $>321$  mg caffeine day<sup>-1</sup> during pregnancy, OR = 1.95, 95% CI = 1.29–2.93, and OR = 2.62, 95% CI = 1.38–5.01, respectively). For caffeine consumption before pregnancy, the OR increased by a factor of 1.10 for each 100 mg caffeine ingested per day. For consumption during pregnancy, the OR increased by a factor of 1.22 for each 100 mg ingested per day. The conclusion was that the incidence of spontaneous abortions was strongly associated with caffeine intake during pregnancy and moderately associated with caffeine use before pregnancy.

The majority of papers that showed an increased risk of spontaneous abortion with caffeine consumption showed associations at levels of  $\geq 300$  mg caffeine day<sup>-1</sup>. In a prospective cohort study by Dlugosz *et al.* (1996), for example, only the highest use of coffee and tea (three or more cups per day, about  $\geq 300$  mg caffeine day<sup>-1</sup>) was associated with an increased risk of spontaneous abortions (OR = 2.63, 95% CI = 1.29–5.34, for coffee; OR = 2.33, 95% CI = 0.92–5.85, for tea). Armstrong *et al.* (1992), in a retrospective study of 35 848 pregnancies in Quebec, Canada, found the percentage of subjects with spontaneous abortions to be 20.4, 21.3, 24.1, 28.1 and 30.9% for persons consuming none, one to two, three to four, five to nine and 10 or more cups per day, respectively. The ORs in these consumption categories were 1.00 (referent), 0.98 (95% CI = 0.93–1.04), 1.02 (0.94–1.12), 1.17 (1.03–1.32) and 1.19 (0.97–1.45), respectively. In this paper, the time lag between the actual abortion and the interview may have introduced errors in recall about the amount of coffee consumed in previous pregnancies. Subjects in this paper were questioned about the incidence of spontaneous abortion and caffeine intake in all previous pregnancies.

Wen *et al.* (2001) studied the association between caffeine consumption and nausea and the risk of spontaneous abortion. The categories of caffeine consumption (based on periodic food frequency questionnaires) were:  $<20$ , 20–99, 100–299 and



$\geq 300$  mg day<sup>-1</sup>. Caffeine consumption was calculated for the periods before pregnancy, in the first trimester of pregnancy, and up to the date of any spontaneous abortion if it occurred before the end of the first trimester. The presence and duration of nausea were monitored. Potential confounders were analysed, including demographic factors, smoking and the consumption of alcohol. Parity and body mass index were also considered. None of these parameters caused any important confounding and, therefore, the data were left unadjusted for these factors. Overall, 7.2 versus 29.6% of the women who experienced any nausea or no nausea, respectively, had spontaneous abortions. In this study, no increased risk of spontaneous abortion was noted with any level of pre-pregnancy intake of caffeine. The data showed that the consumption of caffeine did not increase the risk of spontaneous abortion in women who were already at risk due to a lack of nausea or a reduced frequency/duration of nausea. However, in those women who had nausea in their first trimester and who were consequently at a reduced risk of spontaneous abortion, increased caffeine consumption during the first trimester was associated with abortion. The risk ratios and 95% CIs were: <20 mg caffeine day<sup>-1</sup>, 1.0 (reference category); 20–99 mg day<sup>-1</sup>, 1.8 (0.8–3.9); 100–299 mg day<sup>-1</sup>, 2.4 (0.9–6.2); and  $\geq 300$  mg day<sup>-1</sup>, 5.4 (2.0–14.6). The risk of spontaneous abortion was elevated significantly with a consumption of caffeine  $\geq 300$  mg day<sup>-1</sup>.

Klebanoff *et al.* (1999), using actual serum measurements of paraxanthine, a major caffeine metabolite, showed an increased risk of spontaneous abortion at an estimated 600–1100 mg caffeine day<sup>-1</sup>. In this retrospective study of 591 women who had spontaneous abortions and 2558 matched controls, women with spontaneous abortions had significantly higher serum paraxanthine levels than the controls (752 and 583 ng ml<sup>-1</sup> in women having spontaneous abortions and controls, respectively). The increased risk of spontaneous abortions (OR = 1.9, 95% CI = 1.2–2.8) was noted only in those women with serum paraxanthine concentrations >1845 ng ml<sup>-1</sup>. The authors concluded that the daily intake of caffeine needed to reach 1845 ng paraxanthine/ml serum in a 60-kg woman would be about 600 mg for those who do not smoke and 1100 mg in those who smoke. This would correlate with about six and 11 cups of coffee per day, respectively.

Some studies have revealed the possibility that constituents in coffee or tea other than caffeine may be

related to an increased risk of spontaneous abortion in women (Watkinson and Fried 1985, Srisuphan and Bracken 1986, Dlugosz *et al.* 1996). The one study that accurately measured caffeine consumption (Watkinson and Fried 1985) found no association between caffeine intake and spontaneous abortion, but did find a statistically significant larger proportion of coffee and tea drinkers in the group of women who had spontaneous abortions. Dlugosz *et al.* (1996) found that caffeinated soft drink use (up to three or more cans per day) did not increase the risk of spontaneous abortions. Tea and coffee (at consumption of up to three or more cups of either drink per day) produced similar risks, despite these products having differing caffeine contents.

Although much epidemiological work has been conducted, additional prospective studies that measure actual caffeine intake in the participants and that adjust for potential confounders such as nausea and vomiting during pregnancy would be beneficial. In the absence of these data, however, there appear to be reasonable grounds for limiting the consumption of caffeine to <300 mg day<sup>-1</sup> in women who are, or who are planning to become, pregnant.

### *Foetal growth*

The potential adverse impact of caffeine consumption during pregnancy on foetal growth has been a concern for many years. Caffeine increases the levels of cAMP through inhibition of phosphodiesterases, and the rise in cAMP might interfere with foetal cell growth and development (Karen 2000). Caffeine may also block specific adenosine receptors. As adenosine is involved in maintaining the balance between the availability and the use of tissue oxygen, blockage of its receptors could increase the susceptibility of the cell to hypoxia. Consumption of two cups of coffee has been reported to increase maternal epinephrine concentration and decrease intervillous placental blood flow (Fortier *et al.* 1993). As smoking is closely associated with caffeine consumption, it is important to stress that caffeine and smoking impose similar adverse physiological effects on foetal development (Fortier *et al.* 1993).

Results from epidemiological studies investigating the association between caffeine consumption and foetal growth have been conflicting. Of 18 original epidemiological studies, three indicate an association be-

tween either low birth weight (body weight <2500 g at birth) or intrauterine growth retardation (defined as birth weight <10th percentile of the sex-specific and gestation age-specific distribution of birth weight) and caffeine consumption <300 mg day<sup>-1</sup>. In a population-based study by Fortier *et al.* (1993), caffeine intake by 7025 women living in the Quebec City, Canada, area was not related to low birth weight but was associated with an increased risk of intrauterine growth retardation. For women whose average daily caffeine consumption was 0–10, 11–150, 151–300 or >300 mg, the adjusted ORs for delivering a newborn with growth retardation were 1.00, 1.28 (95% CI = 1.04–1.59), 1.42 (1.07–1.87) and 1.57 (1.05–2.33), respectively. In a Brazilian unmatched case-control study by Rondo *et al.* (1996), results showed that the proportion of mothers who delivered babies with intrauterine growth retardation increased as the average consumption of coffee increased during pregnancy. Compared with mothers whose babies' growth was appropriate for gestation age, the ORs of mothers with babies with intrauterine growth retardation were 1.55 (95% CI = 0.99–2.44), 2.25 (1.34–3.78) and 2.07 (1.14–3.78) for caffeine consumption levels of approximately <140, 141–280 and ≥281 mg caffeine day<sup>-1</sup>, respectively, following adjustment for confounders such as cigarette smoking, alcohol intake and per capita income. Vlajinac *et al.* (1997), in an investigation of the effect of caffeine consumption during the third trimester on birth weight, found that birth weight decreased as caffeine consumption increased at levels ranging from 71 to ≥140 mg day<sup>-1</sup> in non-smokers.

Five studies reported an increased risk for foetal growth retardation in infants whose mothers were exposed to caffeine at dose levels of ≥300 mg day<sup>-1</sup> during pregnancy after adjustment for potential confounders, including cigarette smoking and alcohol consumption (especially binge drinking). In the prospective study by Watkinson and Fried (1985) in which data were collected on maternal use of tea, coffee, caffeinated soft drinks, chocolate bars, chocolate drinks and caffeinated medication, the most marked effects associated with heavy caffeine use (>300 mg day<sup>-1</sup>) were reduced birth weight and small head circumference; the associations were still significant after adjustment for maternal nicotine use. The mean weight of babies born to 12 heavy users was 3158 compared with 3537 g for the remaining sample. The results suggest that daily caffeine intake of ≥300 mg can interfere with normal foetal growth. In a prospective study investigating the effects of

caffeine consumption on intrauterine growth retardation, Martin and Bracken (1987) found that low birth weight was most common among offspring of women consuming >300 mg caffeine day<sup>-1</sup>, the rate being 7.3% compared with the unexposed group rate of 4.1%. Heavy caffeine intake (>300 mg day<sup>-1</sup>) was associated with a 120-g reduction in birth weight compared with the untreated group. Moderate use of caffeine (151–300 mg day<sup>-1</sup>) was also associated with a decrease in birth weight, but to a lesser extent. When a comparison was made with women who had no caffeine exposure, the relative risks (RR) of low birth weight after adjustment for confounding factors (maternal age, ethnicity, education, previous spontaneous abortions, previous stillbirth, weight gain, body mass index, smoking and alcohol intake) were 1.4 (95% CI = 0.70–3.00) for 1–150 mg caffeine day<sup>-1</sup>, 2.3 (1.1–5.2) for 151–300 mg, and 4.6 (2.0–10.5) for >300 mg. Beaulac-Baillargeon and Desrosiers (1987) found that birth weight was significantly less for women who consumed >300 mg caffeine day<sup>-1</sup> and who smoked 15 or more cigarettes per day. In a case-control study by Caan and Goldhaber (1989), the data showed no increased risk of low birth weight with light to moderate consumption of caffeine (<300 mg day<sup>-1</sup>) (adjusted OR = 0.90, 95% CI = 0.4–1.92) but a small but measurable increased risk with heavy consumption of caffeine (>300 mg day<sup>-1</sup>) (adjusted OR = 2.94, 95% CI = 0.89–9.65). One limitation of this study was its small sample size (131 cases, 136 controls). Fenster *et al.* (1991b) found that heavy caffeine consumption of >300 mg day<sup>-1</sup> significantly increased the risk for foetal growth retardation. The mean birth weights for no, light (1–150 mg day<sup>-1</sup>), moderate (151–300 mg day<sup>-1</sup>) and heavy (>300 mg day<sup>-1</sup>) caffeine use were 3327, 3311, 3288 and 3170 g (reduction of 0, 0.5, 1.2 and 4.7%), respectively. Adjusted ORs for low birth weight for women consuming 1–150, 150–300 and 300 mg caffeine day<sup>-1</sup> were 0.78 (95% CI = 0.45–1.35), 1.07 (0.51–2.21) and 2.05 (0.86–4.88), respectively.

Three studies reported a reduction in birth weight for infants born to mothers who consumed caffeine during gestation at 400, 500 or ≥800 mg caffeine day<sup>-1</sup>. Olsen *et al.* (1991), in a study of 11 858 pregnant women in Denmark, found that maternal coffee consumption of four or more cups per day (400 mg caffeine day<sup>-1</sup>) was associated with a moderate decrease in birth weight. The adjusted OR for women consuming 400–700 mg caffeine day<sup>-1</sup> was 1.4 (95% CI = 1.10–1.70); for those consuming ≥800 mg day<sup>-1</sup>,

the OR was 1.2 (0.90–1.80). No dose–response relationship was observed. One explanation for the results might be that individuals who drink many cups of coffee may tend to drink weaker coffee, and therefore the caffeine intake may have been overestimated in the group drinking more coffee. In this study, the women assigned to the control group consumed 0–300 mg caffeine day<sup>-1</sup>. McDonald *et al.* (1992a), in a study of 40 455 pregnancies in Montreal, Canada, found that coffee consumption at levels of 10 or more cups per day was associated with low birth weights and that consumption at levels of five to nine cups per day was associated with lower birth weight for gestational age, after adjusting for such confounders as maternal age, smoking and alcohol consumption. Adjusted ORs for low birth weight at one to two, three to four, five to nine and 10 or more cups per day were 1.05 (95% CI = 0.95–1.16), 1.08 (0.93–1.25), 1.13 (0.92–1.39) and 1.43 (1.02–2.02), respectively. For low birth weight for gestational age, the ORs at one to two, three to four, five to nine and 10 or more cups per day were 1.05 (95% CI = 0.94–1.16), 1.15 (0.99–1.34), 1.34 (1.10–1.65) and 1.39 (0.97–1.98), respectively, when compared with the controls (no coffee consumption). Although Larroque *et al.* (1993) found no clear relation between caffeine consumption and birth weight in different groups of maternal tobacco use, there was a decreasing trend in non-smokers; women who drank >800 mg caffeine day<sup>-1</sup> had infants weighing 187 g less than the infants of those who drank ≤ 400 mg day<sup>-1</sup>, and this difference was at the limit of significance. In this study, non-users and users of <400 mg caffeine day<sup>-1</sup> were combined and used as the control group.

Seven studies reported no association of caffeine consumption with birth weight or foetal growth retardation at levels of 300 to ≥ 400 mg day<sup>-1</sup> during pregnancy. In a study of 12 205 women in the Boston area in the USA, Linn *et al.* (1982) found no relation between low birth weight and coffee consumption of up to four cups per day after controlling for confounders, including smoking and alcohol intake. The adjusted OR among heavy coffee drinkers (four or more cups per day) was 1.19 (95% CI = 0.86–1.65). These negative results suggest that coffee consumption had a minimal effect, if any, on birth weight under the conditions of this study. Brooke *et al.* (1989) found no significant effects of caffeine consumption on birth weight in 1513 women in England after controlling for smoking with caffeine intakes of 0, 1–200, 201–400 and ≥ 401 mg day<sup>-1</sup>. Barr and Streissguth (1991) reported no undesirable changes

in birth weight, length or head circumference for infants born to mothers exposed to caffeine at doses up to 750 mg day<sup>-1</sup> during the entire pregnancy. Godel *et al.* (1992) found no association between caffeine ingestion (>300 mg day<sup>-1</sup>) and birth weight, length or head circumference in the babies of 162 women in northern Canada when the data were adjusted for smoking and alcohol intake. Mills *et al.* (1993), in a prospective study of 423 women in the USA, found that moderate caffeine consumption (≤ 300 mg day<sup>-1</sup>) was not associated with a reduction in early foetal growth. Although heavy caffeine consumption (>300 mg day<sup>-1</sup>) appeared to have a negative effect on intrauterine growth and head circumference, the negative effect was no longer significant after adjusting for other risk factors, notably smoking and maternal age. In a prospective study by Shu *et al.* (1995), caffeine consumption at dose levels up to 300 mg day<sup>-1</sup> (three cups of coffee per day) showed no relation to foetal growth. Although heavy caffeine consumption (≥ 300 mg day<sup>-1</sup>) in the first or second trimester was related to a reduction of crude mean birth weight (93 g for the first trimester, 141 g for the second trimester), the study reported no decrease in foetal growth in any trimester when the data were adjusted for parity, pre-pregnancy weight, income, smoking and nausea. A matched case-control study by Santos *et al.* (1998) found no association between caffeine consumption at an average dose level of approximately 150 mg day<sup>-1</sup> and increased risk of low birth weight or intrauterine growth retardation.

The interaction of caffeine consumption and smoking and their association with low birth weight were also reported. Several studies have found a marked positive correlation between smoking and caffeine intake, including Godel *et al.* (1992), Fortier *et al.* (1993), and Vlajinac *et al.* (1997). Beaulac-Baillargeon and Desrosiers (1987) found that birth weight was not statistically different with a caffeine consumption of >300 mg day<sup>-1</sup> for non-smokers and women who smoked one to 14 cigarettes per day, but the birth weight of babies of women who consumed ≥ 300 mg caffeine day<sup>-1</sup> and smoked 15 or more cigarettes per day was significantly lighter (206 g less) than that of babies whose mothers consumed less caffeine. Contradictory results were found by Vlajinac *et al.* (1997): that caffeine intake had an effect only in non-smokers. Among non-smokers, women whose daily caffeine intake was 71–140 mg day<sup>-1</sup> had infants weighing 116 g less than the infants of women whose caffeine consumption was 0–10 mg day<sup>-1</sup>. For

those whose caffeine intake was  $\geq 140 \text{ mg day}^{-1}$ , the decrease in birth weight was 153 g. The authors suggested that the effect of smoking is more powerful than that of caffeine, so that caffeine intake does not produce any noticeable effect in women who smoke.

It is difficult to establish the cause of the inconsistencies in the results of studies investigating the association between caffeine consumption and foetal growth. They may have resulted from recall bias, particularly in retrospective studies, incomplete information on amounts and sources of caffeine consumption, misclassification of caffeine exposure, inadequate control for confounders or simply unknown study bias. In two studies (Olsen *et al.* 1991, Larroque *et al.* 1993), investigators combined non-users and users (consuming  $<400 \text{ mg caffeine day}^{-1}$  in Larroque *et al.* 1993) and used them as the control group. If, for example, exposure to caffeine at dose levels  $<400 \text{ mg day}^{-1}$  is associated with reduced birth weight, then comparing this control group with heavier users may obscure any positive association. Despite inconsistencies in the results, the persistent association between caffeine consumption during pregnancy and low birth weight observed in eight original studies strongly suggests that caffeine may adversely affect foetal growth. This conclusion is supported by a meta-analysis study incorporating seven original studies and involving a total of 64 268 pregnancies, which reported a statistically significant increase in the risk for low birth weight babies in pregnant women consuming  $>50 \text{ mg caffeine day}^{-1}$  (Fernandes *et al.* 1998). It should be indicated that due to the nature of data presentation in individual studies used in meta-analysis, the authors were unable to adjust for potential confounders (maternal age, smoking, alcohol intake or other confounders) that may have contributed to the final result.

Based on the above evaluated data, despite inconsistencies in the results, it is concluded that caffeine consumption during pregnancy at dose levels of  $\geq 300 \text{ mg day}^{-1}$  may interfere with foetal growth (decrease in birth weight or intrauterine growth retardation), particularly in smokers or heavy alcohol drinkers.

### *Preterm delivery*

Relatively few epidemiological studies are available that address an association between caffeine con-

sumption and preterm delivery. Nine of 11 studies reviewed showed that caffeine consumption at dose levels up to  $\geq 300 \text{ mg day}^{-1}$  was not an important risk factor for preterm delivery (Linn *et al.* 1982, Watkinson and Fried 1985, Fenster *et al.* 1991b, Olsen *et al.* 1991, McDonald *et al.* 1992a, Fortier *et al.* 1993, Mills *et al.* 1993, Pastore and Savitz 1995, Santos *et al.* 1998). In the case-control study performed by Pastore and Savitz (1995) to investigate the association between caffeinated beverage consumption and preterm delivery in women from North Carolina, USA, consumption at the 1–150 mg caffeine day<sup>-1</sup> level was associated with a moderately increased risk of preterm delivery, although there was no association between high levels of caffeine consumption and preterm delivery. The lack of a dose-response relationship strongly suggests that there is no association between caffeine consumption at dose levels as high as  $\geq 400 \text{ mg day}^{-1}$  and preterm delivery.

Only two studies (Berkowitz *et al.* 1982, Williams *et al.* 1992) suggested a possible relation between caffeine consumption ( $\geq 300 \text{ mg day}^{-1}$ ) and preterm delivery. Although Berkowitz *et al.* (1982) observed no association between coffee consumption (four or more cups per day) and preterm delivery in their case-control retrospective study, tea drinking, especially four or more cups per day in the first trimester, resulted in a slightly increased risk of preterm delivery (OR = 2.0, 95% CI = 1.0–4.0). The authors postulated that some other component of tea, if consumed in sufficient amounts, may have an adverse effect on gestation age. In Williams *et al.* (1992), women who consumed three or more cups of coffee per day during the first trimester had a 2.2-fold increase in risk of preterm premature rupture of the membranes compared with women who consumed two or fewer cups of coffee per day (OR = 2.2, 95% CI = 1.5–3.5). When only coffee drinkers were examined, there appeared to be a linear trend in the risk of preterm premature rupture of the membranes as coffee consumption increased. Maternal coffee consumption had relatively little relation to the risk of spontaneous preterm labour not complicated by premature rupture of the membranes. Women who drank three or more cups of coffee per day experienced a 1.4-fold increase in the risk of spontaneous preterm labour not complicated by premature rupture of the membranes compared with women who drank two or fewer cups of coffee per day (adjusted OR = 1.4, 95% CI = 1.0–1.9). It should be pointed out that low socio-economic status, history of adverse pregnancy outcome and antepar-

tum haemorrhaging have been reported consistently as risk factors of preterm delivery (Williams *et al.* 1992). Other factors, such as young and advanced maternal age, low maternal weight before pregnancy, and smoking during pregnancy, may also influence pregnancy outcome.

Based on the above evaluated data, it is concluded that caffeine consumption during pregnancy at dose levels of  $\leq 300 \text{ mg day}^{-1}$  is unlikely to have an adverse effect on the length of gestation (preterm delivery).

### *Congenital malformations*

The limited available epidemiological data show no increase in the incidence of congenital morphological malformations in infants born to mothers who consumed three to 10 or more cups of coffee per day ( $300\text{--}1000 \text{ mg caffeine day}^{-1}$ ) during the entire pregnancy.

Rosenberg *et al.* (1982) examined the association between drinking caffeine-containing beverages and five malformations (inguinal hernia, oral clefts, cardiac defects, pyloric stenosis, neural tube defects) in a case-control study of 2030 children in Canada and the USA. No association was found between coffee consumption at levels up to  $\geq 400 \text{ mg caffeine day}^{-1}$  and any of the malformations investigated. In a case-control study of 706 children with birth defects in Finland (central nervous system defects, orofacial clefts, musculoskeletal defects, cardiovascular malformations), coffee consumption (up to  $1000 \text{ mg caffeine day}^{-1}$ ) showed no significant association with malformations observed under the conditions of the study (Kurppa *et al.* 1983). Linn *et al.* (1982) reported no consistent association between coffee consumption (up to four or more cups per day) and the occurrence of malformations in a retrospective study of 12 205 women in the Boston area in the USA. Similarly, Olsen *et al.* (1991) found no association between coffee or tea consumption up to four or more cups per day and the occurrence of malformations in a Danish study.

Narod *et al.* (1991) reviewed the results from many epidemiological studies investigating potential teratogenic effects of caffeine and found that available data do not implicate coffee and/or caffeine as a likely human teratogen in the classical sense (development

of morphological malformations), even at dose levels up to eight cups of coffee per day.

In one positive study, McDonald *et al.* (1992b) analysed the association of coffee consumption with congenital defects for 80 319 pregnancies in Montreal, Canada. A significant increase in the incidence of heart defects (RR = 1.52, 95% CI = 1.1–2.2) was observed among the children of women who drank three or more cups of coffee per day. However, no specific type of heart defect was over-represented in this group when compared with defects in babies born to women who did not drink coffee.

There is therefore little evidence to support the hypothesis that moderate consumption of caffeine during pregnancy can present a teratogenic (morphological malformations) risk in humans. It should, however, be noted that available data from reviewed literature show that caffeine can be teratogenic in animals when ingested at very high dose levels ( $\geq 80 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ ) in comparison with the range of typical human intakes (e.g. Collins *et al.* 1981, James 1991a, Purves and Sullivan 1993).

### *Postnatal development*

The foetus is exposed to caffeine ingested by the pregnant mother, since caffeine is rapidly absorbed from the gastrointestinal tract, readily crosses the placenta, and is distributed to all foetal tissues. In addition, exposure of the foetus to caffeine is enhanced because caffeine's half-life is markedly increased in the foetus and pregnant women in comparison with non-pregnant adults and older children (Dalvi 1986, Dlugosz and Bracken 1992, Eskenazi 1993). Because of the rapid growth that occurs during the late prenatal period, the impact of chronic caffeine exposure may be far greater than at any other time of life.

In a cohort study of 453 infants, caffeine ingested during pregnancy at dose levels up to  $444 \text{ mg day}^{-1}$  did not adversely affect infant size at 8 months of age (Barr *et al.* 1984). A prospective study of 123 infants from three hospitals in Ottawa, Canada, showed that caffeine consumption at doses of  $\geq 300 \text{ mg day}^{-1}$  had no adverse effects on postnatal growth at 12 and 24 months of age following adjustment for relevant confounders (Fried and O'Connell 1987). Barr and Streissguth (1991) investigated the effects of prenatal caffeine exposure on postnatal development from

birth to 7 years of age and found that long-term prenatal exposure (during the entire pregnancy) to caffeine at dose levels ranging from 174 to 740 mg day<sup>-1</sup> had no adverse effects on the physical and/or behavioural development (e.g. orientation, reactivity, IQ, fine and gross motor skills) of children during the first 7 years of life.

Toubas *et al.* (1986) demonstrated that maternal exposure to caffeine (350 ± 370 mg day<sup>-1</sup>, non-smokers, 185 cases) during gestation resulted in an increased incidence of central and obstructive infantile apnoea (cessation of breathing). The incidence of these symptoms was greater in infants born to mothers who smoked (85 cases) and consumed caffeine at dose levels of 610 ± 517 mg day<sup>-1</sup>.

Two studies assessed the association between caffeine consumption and the risk of sudden infant death syndrome (SIDS). In Ford *et al.* (1998), heavy consumption of caffeine (≥ 400 mg day<sup>-1</sup>, equivalent to four or more cups of coffee per day) was associated with a significantly increased risk for SIDS after adjustment for likely confounders. Although the results of this study have been criticized (Leviton 1998) on the grounds that parental smoking was not properly assessed, the authors responded that supplementary analysis of the data supported their results. The second study (Alm *et al.* 1999) found no association between caffeine ingestion and increased risk of SIDS at dose levels up to 800 mg day<sup>-1</sup> during and after pregnancy after adjustment either for smoking or for maternal age, education, parity and smoking in the first trimester. Many factors have been identified that may increase the risk of SIDS including, low maternal age, high live birth order, foetal prone sleep position, maternal smoking during pregnancy and postnatal exposure to passive smoke (MacDorman *et al.* 1997, Oyen *et al.* 1997, l'Hoir *et al.* 1998). The two factors, maternal smoking during pregnancy and infant prone sleeping position, appeared to be the major risk factors in SIDS (Golding 1997, MacDorman *et al.* 1997, Brouillette 2001, Nelson and Taylor 2001, Paris *et al.* 2001). Based on the data presented, it is difficult to establish what risk, if any, intake of caffeine during pregnancy may play in SIDS.

Based on limited epidemiological data, it can be concluded that it is unlikely that moderate intake of caffeine (≤ 300 mg day<sup>-1</sup>) by pregnant and nursing mothers would pose adverse effects on postnatal development.

## Summary and conclusions

Caffeine is widely consumed at different levels by most segments of the population. Both the public and the scientific community have expressed concern about the potential for caffeine to produce adverse effects on human health. The possibility that caffeine ingestion adversely affects human health was investigated based on reviews of published (primarily) human studies obtained through a comprehensive literature search. The following potential adverse effects of caffeine on human health were investigated: general toxicity, cardiovascular effects, effects on calcium balance and bone status, behavioural effects in adults and children, carcinogenic potential, genotoxic potential, and reproductive effects, including pre- and postnatal development. It should be pointed out that review of some of the epidemiological studies was complicated by one or more methodological issues, such as inadequate measurement of caffeine intake; a lack of consideration of all sources of caffeine intake; a lack of consideration of caffeine intake before study; the lack of distinction made between different types of preparation and different strengths of coffee in most studies; inadequate control for the possible confounding effects of variables such as smoking, alcohol consumption, age, nutrition and lifestyle factors in some studies; the low response rates in several studies; biased selection of adequate controls because of self-selection into groups of drinkers and non-drinkers of coffee; recall bias in retrospective studies; and insufficient statistical power in some of the studies. Despite these issues, the majority of the reviewed studies provided important and useful data with which to assess the potential effects of caffeine on human health.

Based on the data reviewed, it can be concluded that there is ample evidence indicating that for the general population of healthy adults, moderate caffeine intake at a dose level of 400 mg day<sup>-1</sup> is not associated with adverse effects such as general toxicity, cardiovascular effects, changes in adult behaviour, increased incidence of cancer and effects on male fertility. Nor are moderate intakes of caffeine associated with adverse effects on bone status and/or calcium balance if adequate intakes of calcium are being consumed. Data have also shown that reproductive-aged women can be defined as an 'at risk' group who may require specific advice on moderating their caffeine intake. It is therefore recommended that caffeine intake for women who plan to become pregnant and for women

during gestation should not exceed  $300 \text{ mg day}^{-1}$ , equivalent to  $4.6 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  in a 65-kg person.

Children are another at-risk population identified in the literature. While data are lacking on adolescent children, some studies exist for pre-adolescents. Although this literature has its shortcomings, findings of altered behaviour, including anxiety, are noted in a variety of studies using caffeine in children. The existing literature is difficult to compare due to differing methodologies as well as inadequacies in methodology in some cases; however, effects have been noted down to the lowest level of administered caffeine used (effects on state anxiety, correlated with salivary caffeine levels at an intake of  $2.5 \text{ mg kg}^{-1} \text{ bw}$ , in Bernstein *et al.* 1994). The body of evidence, in totality, suggests that caffeine can elicit behavioural effects in children. Owing to these findings, as well as the fact that the nervous system in children is continually developing and the lack of available information on the longer-term effects of caffeine in this population, a cautious approach is warranted. It is judged that in the absence of more robust data associated with low levels of administered caffeine, an upper intake of  $2.5 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  is an amount on which to base risk assessments of caffeine consumption in children.

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