REPORT

FROM THE EXPERT WORKING GROUP

ON

THE SAFETY ASPECTS OF DIETARY CAFFEINE

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Important note

This paper was prepared by the Expert Working Group on Caffeine with the assistance of staff from the Australia New Zealand Food Authority. All members listed below participated in the working group's deliberations. Professor Jack James did not participate in the finalisation of the report, and should not be regarded as necessarily supporting it. Professor James has provided comments on the final Report which are provided as a supplement at the back of this report.

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Acknowledgment

The Australia New Zealand Food Authority appreciates the knowledge and expertise contributed by the above and would like to thank them for their valuable contribution to the Expert Working Group on caffeine.

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PREAMBLE

The Australia New Zealand Food Authority (ANZFA) established an Expert Working Group in November 1999 to examine the wider safety aspects of dietary sources of caffeine.

The conclusions of the Expert Working Group will be considered by ANZFA in relation to the assessment of specific applications to vary the permissions for the addition of caffeine to food/beverages in relevant food standards in the Australian Food Standards Code. Current applications for which advice on caffeine is being sought are, an application to extend the use of caffeine in all soft drinks (A344) and, an application to establish a maximum level for caffeine in energy drinks (A394).

The conclusions of the Expert Working Group may also be relevant to subsequent applications to vary standards for other foods containing caffeine.

1. The Regulation of Caffeine in Foods (Soft Drinks, Energy Drinks and Sports Foods) in Australia, New Zealand and Internationally

- **Soft drinks**

Australian Food Standards Code

The Australian Food Standards Code restricts the addition of caffeine to kola-type soft drinks, flavoured cordials and flavoured syrups. In these drinks, the total caffeine content must not exceed 145 mg/kg (36mg/250ml serve) in the drink as consumed. The Code does not prescribe limits for naturally occurring caffeine in food - for example, tea, coffee and guarana. The caffeine levels in these foods will not normally exceed 100 mg in a standard serving.

New Zealand Food Regulations
In New Zealand, caffeine may be added to any soft drinks, and a maximum level of 200 mg/kg is prescribed. It is also permitted to be used as a flavouring in any other non-alcoholic beverages where flavourings are permitted, with no maximum level prescribed.

International Regulations
Internationally, caffeine is permitted in soft drinks at levels ranging from 150 to 300 mg/kg. The Codex Alimentarius Commission does not prescribe a level for caffeine.

- **Energy Drinks and Sports foods**

Energy drinks are non-alcoholic beverages characterised by the addition of "energy enhancing" ingredients. These may include a number of water-soluble B vitamins, amino acids and other substances, and caffeine. The caffeine is added as pure caffeine or as guarana, a herbal caffeine source. Most energy drinks do not exceed levels of caffeine of about 80mg/250 mL. This caffeine level in energy drinks is comparable to the caffeine level in a strong cup of coffee.

Guarana is often added to energy drinks either in combination with caffeine or on its own. Guarana is made from the crushed seeds of a native Brazilian plant. The stimulant effect of guarana is related to its caffeine content. A 1 gram dose of guarana will contain about as much caffeine as a medium strength cup of coffee.

Energy drinks are promoted to young people to boost energy and vitality particularly in times of added stress; in New Zealand, they are also promoted as alternatives to alcoholic drinks. Red Bull Energy drink is one of over 20 energy drinks currently for sale on the New Zealand market. Energy drinks are available in over 30 countries, and are well established in Europe and the United States of America.

New Zealand Food Regulations

Energy drinks are regulated in New Zealand under the *Dietary Supplements Regulations* 1985, made under the Food Act 1981 but are not regulated under *New Zealand Food Regulations* 1984. The current New Zealand Food Regulations and the Dietary Supplements Regulations do not require that a food or dietary supplement containing guarana is labelled as a source of caffeine.

Australian Food Standards Code

The Australian *Food Standards Code* does not have a standard that covers energy drinks. Prior to the introduction of the Trans Tasman Mutual Recognition Arrangement (TTMRA) in 1998, the current formulations of energy drinks could not be legally sold in Australia.

Products regulated under the New Zealand Dietary Supplements Regulations are considered in Australia as either foods or therapeutic goods; there is no separate dietary supplement category.

TTMRA permits the importation of energy drinks from or through New Zealand providing they comply with the New Zealand Dietary Supplements Regulations.

Sports Foods.

As noted above energy drinks are regulated in New Zealand under the *Dietary Supplements Regulations* 1985. However, similar products are manufactured in Australia following a re-formulation (and adherence to specified upper limits for ingredients such as vitamins and minerals) of the product under Standard R10-Formulated Supplementary Sports Foods. The caffeine content of such products is from guarana which is legally a food in the Australian regulations and so escapes the restrictions placed on addition of caffeine. Foods can be mixed with other foods without special permission under food laws.

2. Applications currently being assessed by ANZFA

- **Application to extend the use of caffeine in all soft drinks (A344)**

ANZFA received an application on 9 July 1997 from Kensington Swan, a New Zealand legal firm, to amend the Food Standards Code so as to permit the same uses for caffeine in Australia that are currently permitted in New Zealand. The application was subsequently amended to limit the request to an extension of use of caffeine into all soft drinks at the maximum permitted level of 145 mg/kg.

ANZFA has now stopped-the-clock on application A344 (17 August 1999) awaiting the submission of new data from the applicant arising from the submissions at inquiry and in addition the deliberations from an Expert Working Party (see below).

- **Application for Red Bull energy drink (A394)**

ANZFA is currently considering an application from Red Bull to develop appropriate regulatory provisions for energy drinks within the *Food Standards Code*. The current situation enables product to be imported from New Zealand into Australia but does not permit such energy drinks (in their current formulation) to be manufactured in Australia for domestic consumption because New Zealand food or dietary supplement regulations are not recognised for Australian domestic manufacture.

Although revised formulations of energy drinks could be made in Australia under the Food Standards Code, no single food standard provides all the permissions sought by manufacturers of these drinks.

3. Formation of the Expert Working Group

In order to broaden scientific input into the assessment of application A344 and to further address community concerns regarding the effects of caffeine (particularly in relation to behavioural effects in children), ANZFA established an Expert Working Group.

- **Nomination to the Expert Working Group**

On 21 September 1999, ANZFA sought nominations of scientific or clinical experts in the area of toxicology and/or pharmacology (particularly behavioural aspects) to form the basis of the Expert Working Group. Nominations were received from State and Territory Governments, industry, consumer organisations and the health sector. The following six individuals, nominated by various groups were appointed to the Expert Working Group:

Group Member	**Nominated by:**
Dr Alex Proudfoot	ANZFA (Chair)
Prof. Paul Smith	New Zealand Ministry of Health

Prof. Andrew Smith	Australasian Soft Drink Association
Prof. John Miners	South Australian Department of Health
Prof. John McNeil	ANZFA (to provide clinical perspective)
Prof. Jack James	Consumer Food Network of Australia and New Zealand.

On 11 November 1999 ANZFA formally established the Expert Working Group on caffeine. The group indicated both their willingness to participate, and their availability between the period November 1999 to March 2000. The report of the Expert Group will be considered as part of developing a final position on Applications A344 and A394.

ANZFA is currently in the process of establishing a reference group to assist with the development of appropriate regulatory policy on caffeine in food. ANZFA is currently seeking nominations of people with expertise in the areas of public health/risk management from State and Territory Governments, industry, consumer organisations and/or the health sector to be part of the reference group. ANZFA intends to select from these nominations a group of approximately 5 people to ensure there is an appropriate representation from all sectors of the community. Nominees would need to be available to undertake work **between June and mid July 2000.**

TERMS OF REFERENCE OF THE EXPERT WORKING GROUP

The Australia New Zealand Food Authority (ANZFA) requests advice from relevant scientific and clinical experts to assist ANZFA with recommendations on the public health and safety aspects of the addition of caffeine to food.

This advice will be used to further develop ANZFA's previous extensive review of the safety of caffeine in soft drinks as part of Application A344. Therefore, advice on the following is requested:

(1) The potential for acute toxicological/pharmacological effects of caffeine at low doses (in particular behavioural effects in children);

(2) The potential for an addictive effect of caffeine; and

(3) identification of any other hazards (eg long-term health effects) of caffeine at low doses.

Although the above terms of reference would incorporate the effects of caffeine in different age groups it would be envisaged that a particular focus would be placed on children.

Given the importance of these matters and their concerns to the State/Territory Health Departments, public health associations and consumers the Expert Working Group is requested to provide this advice by the end of **March 2000**.

ANZFA gave an extension of this time in order for the Expert Working Group to complete the report.

EXECUTIVE SUMMARY

The Australia New Zealand Food Authority (ANZFA) established an Expert Working Group (consisting of external experts) to examine the wider aspects of the safety of dietary sources of caffeine.

The task and terms of reference for the group were to examine the potential for acute toxicological/pharmacological effects at low doses of caffeine (Term of Reference A), the potential for addictive effects (Term of Reference B) and identification of any other caffeine-related hazards particularly in children (Term of Reference C).

The conclusions from the Expert Working Group are as follows:

Term of Reference A

Several variables need to be considered when interpreting studies with caffeine. These include the pharmacokinetics (eg age and sex differences, pregnancy, liver disease, diet, smoking and concomitant drug therapy), the source of caffeine (eg caffeinated beverages such as coffee may have physiological effects related to other constituents), the study design, the population studied and the sample size.

It would be valuable to have data which would enable dose-response and plasma concentration-response curves to be established for different effects (end-points). However, it appears that the relationship between dose and physiological response is continuous down to the lowest levels studied (although these effects are increasingly subtle as dosage is reduced). A 'no effect' level has not been identified. It is likely that caffeine causes subtle effects at very low dose levels, although their detection is ultimately dependent on the sensitivity of indicators and tests employed.

Although larger controlled studies are required to confirm the dose-related effects of low-dose caffeine, the following conclusions can be drawn from the available data:

- There are reports of enhanced performance and mood effects at doses of 37.5mg (0.54 mg/kg bw/day in 70 kg adults);

- There are reports of increased anxiety levels in children at doses of 95mg (3 mg/kg bw/day in children aged 5-12 years with a mean bodyweight of 32kg) and at 210mg in adults (3 mg/kg bw/day in 70 kg adults; and

- Caffeine has been reported to reduce the ability to sleep at doses of 100mg (1.4 mg/kg bw/day in 70 kg adults) at bedtime.

In conclusion, in addressing term of reference A, the threshold dose for possible behavioural effects in children remains unclear and it is recognised that further studies are needed to elucidate the potential effects of caffeine in children at doses that may be ingested from dietary sources.

Term of Reference B

It is concluded that caffeine at doses typically consumed in the diet may lead to withdrawal effects and some physical dependence in adults. The prevalence of such effects has been variable, as has the interpretation and their intensity is minimal in most individuals. Further research will be required at doses typically consumed in the diet to examine whether similar withdrawal effects and physical dependency occurs in children.

Term of Reference C

It would appear that a precise link between caffeine contributing to cardiovascular disease has not been established. The published literature provides little evidence that caffeine in typical dosages consumed in the diet contributes to hypertensive disease.

If it is assumed that caffeine use in childhood lays the foundations for life-long use, there may be some grounds for concern that the consumption of caffeine-containing substances by children could be considered to be undesirable. At this stage it is not possible to conclude that patterns of caffeine consumption established early in life can contribute to negative long-term health outcomes in children and that effects observed in adults can be extrapolated to children.

REPORT FROM THE EXPERT WORKING GROUP ON CAFFEINE

TERM OF REFERENCE A

The potential for acute toxicological/pharmacological effects of caffeine at low doses (in particular behavioural effects in children).

A1.0 Pharmacological effects of caffeine

A1.1 Caffeine metabolism

Five primary metabolic pathways contribute to caffeine (1,3,7-trimethylxanthine) metabolism in adults (Miners and Birkett, 1996; Miners and McKinnon, 2000). The first three, namely, (1) N3-Demethylation to form paraxanthine (PX; 1,7-dimethylxanthine), (2) N1-demethylation to form theobromine (TB; 3,7-dimethylxanthine) and (3) N7-demethylation to form theophylline (TP; 1,3-dimethylxanthine) account, on average, for 79.6%, 10.8% and 3.7%, respectively, of caffeine metabolism *in vivo* (Lelo *et al*, 1986a). The last two, namely, (4) formation of the C8-hydroxylated metabolite 1,3,7-trimethyluric acid (1,3,7-TMU), the C8-N9 bond scission product 6-amino-5-(N-formylmethylamino)-1,3-dimethyluracil (1,3,7-TAU), and (5) renal clearance of unchanged drug together account for the remainder (*ca* 6%) of caffeine elimination (Figure 1).

Once formed, PX, TP and TB are subject to extensive metabolism (Miners and Birkett, 1996). Each dimethylxanthine can undergo two separate N-monodemethylations to form the corresponding monomethylxanthines (*ie* 1-, 3- and 7-methylxanthine; 1-, 3- and 7-MX). Further oxidation, by way of 8-hydroxylation, of 1-MX and 7-MX, but not 3-MX, produces 1- and 7-methyluric acid (1- and 7-MU), respectively. PX, TB and TP similarly undergo 8-hydroxylation giving rise to the respective dimethyluric acid (1,7-, 3,7- and 1,3-DMU). C8-N9 bond scission, to form a dimethylaminouracil (DAU), occurs only for those dimethylxanthines methylated at N7. Thus, PX and TB are converted to 1,7- and 3,7-DAU, respectively. It is believed that 5-acetylamino-6-formylamino-3-methyluracil (AFMU) forms together with 1-MX during the N7-demethylation of PX (Lelo *et al*, 1989). Internal rearrangement or acetylation of a putative unstable ring-opened intermediate results in the formation of 1-MX and AFMU, respectively. Deformylation of AFMU produces 5-acetyl-6-amino-3-methyluracil (AAMU). The relative formation of each precursor dimethylxanthine and the extent of the separate secondary biotransformation reactions determine the proportions of the various caffeine metabolites excreted in urine *in vivo*. As would be expected, those compounds derived from PX, whose formation accounts for approximately 80% of caffeine clearance, are the most abundant metabolites. In adult males for example, N7-demethylation products (*ie* 1-MX, 1-MU, AFMU) account for approximately 60% of all metabolites formed from caffeine.

The pattern of caffeine urinary metabolite excretion in children over six months of age is similar to that observed in adults (Callahan *et al*, 1983; Campbell *et al*, 1987; Carrier *et al*, 1988; Ullrich *et al*, 1992), although most of the studies in children appear not to have investigated the excretion of certain minor metabolites (especially

di- and tri-methylaminouracils). In particular, metabolites derived from PX are the major caffeine-derived products in urine (Carrier *et al*, 1988). Furthermore, the proportion of the dose of caffeine excreted in urine unchanged is low in both children and adolescents (Carrier *et al*, 1988; Ullrich *et al*, 1992). As in adults, it is therefore clear that caffeine is extensively metabolised in children and in adolescents and that the N3-demethylation pathway (to form PX and its subsequent metabolites) is the major route of elimination in these groups.

Human liver microsomal kinetic and inhibition techniques and the use of recombinant cytochromes P450 (CYP) have demonstrated that CYP1A2 is the enzyme responsible for the conversion of caffeine to PX, TB and TP in adult humans (Tassaneeyakul *et al*, 1992 and 1994). Available evidence also suggests that CYP1A2 catalyses the N1- and N7-demethylations of PX and all pathways of TP metabolism (Birkett and Miners, 2000). Both CYP1A2 and CYP2E1 contribute to TB metabolism (Gates and Miners, 1999). CYP1A2 activity is inducible by polycyclic aromatic hydrocarbons, and hence the clearances of drugs metabolised by CYP1A2 (including caffeine and TP) are increased in cigarette smokers (Birkett and Miners, 2000; Miners and McKinnon, 2000).

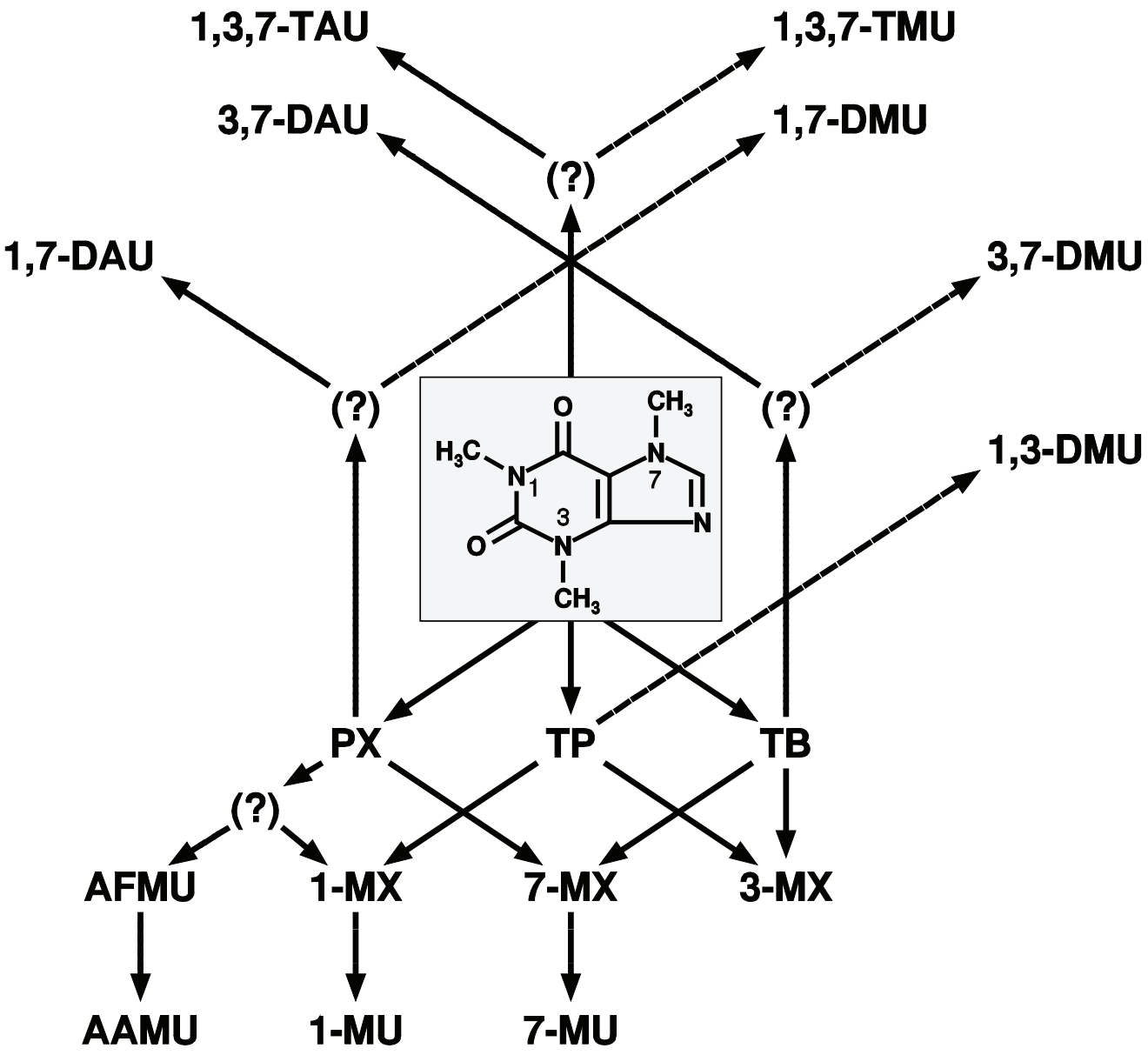

FIGURE 1: Pathways of caffeine metabolism in humans. See text for abbreviations.

A1.2 Caffeine pharmacokinetics

Caffeine pharmacokinetics are well characterised in adults and neonates, but data for children are limited. Ranges for reported mean pharmacokinetic parameters in healthy young adults following oral administration of caffeine are: apparent oral clearance (CL), 0.98 – 2.07 ml/min.kg; volume of distribution (V), 0.7 – 1.3 l/kg; elimination half-life ($t_{½}$), 4.1 – 6.4 hr (Blanchard and Sawers, 1983; Lelo *et al*, 1986b; Newton *et al*, 1981). There is also evidence of dose-dependent kinetics in adults (Denaro *et al*, 1990).

An investigation of the maturation of caffeine elimination in infancy found that caffeine clearance approximated adult values around 4.5 months after birth, but was higher at 6 months of age (Aranda *et al*, 1979). Caffeine clearance values reported for two infants aged about 6 months were 2.61 and 8.45 ml/min.kg. Mean values of $t_{½}$ and V were 2.6 hr and 1.1 l/kg, respectively. Setchell *et al* (1987) reported mean

caffeine $t_{½}$ values of 5.4 hr and 2.9 hr, and mean clearance values of 1.92 ml/min.kg and 10.49 ml/min.kg for adults and children, respectively. However, details of study design and subjects (age, number) were lacking.

Indirect evidence supports enhanced caffeine elimination in children compared to adults. Rate of excretion of $^{13}CO_2$ after a dose caffeine labelled with ^{13}C at the N3-methyl group (referred to as the caffeine breath test, or CBT) reflects the rate of caffeine N3-demethylation (*ie* the conversion of caffeine to PX, the major metabolic pathway) *in vivo*. Labelled CO_2 exhalation has been shown to be about 2-fold higher in children aged 3-9 years compared to adults (Lambert *et al*, 1986). When data were analysed according to gender, rate of labelled-CO_2 formation was higher (by approximately 20%) in male children than in female children. The rate of caffeine N3-demethylation declined with increasing age over 9 years. Gender related differences were again apparent, with CBT values declining with age more rapidly in females than males. Another indirect measure of caffeine by N3-demethylation is the ratio of (AFMU + 1-MX + 1MU) to 1,7-DMU excreted in urine, commonly referred to as the caffeine metabolic ratio (CMR) (Tang and Kalow, 1996). Mean values of the CMR in children aged 3-7 years (8.3) and 7-11 (7.4) are significantly higher than for adults in the age range 18-65 years (4.7) (Campbell *et al*, 1987). CMR values in children approach those observed for smoking adults (8.5 – 9.4).

As noted previously, CYP1A2 is the enzyme responsible for both CA and TP metabolism in humans (Birkett and Miners, 2000; Miners and McKinnon, 2000). It is well established that TP clearance in children is about double that of non-smoking adults, while $t_{½}$ is approximately halved (Grygiel and Birkett, 1980; Ogilvie 1978).

In summary, available data suggests that pathways of caffeine metabolism are similar in adults and children, with CYP1A2-catalysed N3-demethylation dominating. The clearance of caffeine is up to 2-fold higher in prepubescent children than in non-smoking adults, and declines with sexual maturation. Caffeine $t_{½}$ appears to be correspondingly shortened in children. There is no evidence to suggest that the volume of distribution or plasma protein binding of caffeine differs between children and adults. The elimination of the primary caffeine metabolites PX and TP (and to some extent TB) would similarly be expected to be enhanced in children since CYP1A2 also catalyses the metabolism of these compounds.

A1.3 Pharmacodynamic effects and mechanisms of action

At micromolar (μM) concentrations, release of intracellular calcium and inhibition of cyclic nucleotide phosphodiesterases can be largely excluded as potential mechanisms of action for caffeine (Fredholm *et al*., 1999). Caffeine produces its effects almost entirely via its blockade of adenosine A_1 and A_{2A} receptors, both of which are G-protein-coupled. Activation of A_1 receptors results in the inhibition of adenylate cyclase and of some calcium channels (N- and Q-type), and the activation of some potassium channels and phospholipases C and D. Activation of A_{2A} receptors, by contrast, results in activation of adenylate cyclase and of some calcium channels (L-type) (Fredholm *et al*., 1999). It is particularly interesting that caffeine has largely opposing actions on these two types of receptors.

The effects of caffeine on adenosine receptors result in secondary effects on a variety of other neurotransmitter systems, including noradrenaline, dopamine, serotonin,

acetylcholine, glutamate and GABA (Fredholm *et al*., 1999). However, particularly important may be the interaction between A_{2A} receptors and D_2 dopamine receptors, since blockade of A_{2A} receptors may enhance the action of dopamine at D_2 receptors. The blockade of A_1 receptors, on the other hand, affects glutamatergic input to the striatum (Fredholm *et al*., 1998).

There seems to be some general agreement that low oral doses (80mg or 1 mg/kg bw/day in 70 kg adults) of caffeine reduce the activity of striatopallidal neurons in the striatum and nucleus accumbens, although caffeine produces widespread changes in many areas of the CNS, including changes in the expression of immediate early genes (Svenningsson *et al*., 1998; Harlan and Garcia, 1998; Bennett and Semba, 1998; Fredholm *et al*., 1999).

Other studies have suggested that caffeine at low doses (approximately 200 mg/person) can activate components of the pituitary-adrenocortical response: increasing ACTH release and cortisol production (Lovallo *et al*, 1996), affect the melatonin system and temperature levels (Wright *et al*, 1997) and induce an insulin dependent rise in blood glucose levels (Pizziol *et al*, 1998).

A2.0 Behavioural and health effects of caffeine

A2.1 Effects of low dosage

A2.1.1 Definition of low, moderate and high dose

Low doses of caffeine refer to daily intakes in the range 80-250 (1.1-3.5 mg/kg bw/day for 70 kg adults). Moderate doses of caffeine refer to daily intakes of caffeine in the range 300-400 mg/day in adults (ie 4-6 mg/kg bw/day in 70kg adults). High dose refers to intakes of caffeine greater than 500 mg/day (7 mg/kg bw/day in 70 kg adults).

However, the daily intake of caffeine for adults varies enormously across the world, from 210-238 mg/day in the US and Canada to greater than 400 mg/day in Sweden and Finland. Therefore, although the average intake globally is said to be approx. 70-76 mg/person/day, the average intake for individual countries varies dramatically (see Fredholm *et al*., 1999 for a review). Therefore, the definition of 'low-' and 'high-dose' caffeine is problematic and it is important to quantify the dose in all studies.

Data from Australia suggest that the average intake in adults is approx. 232 mg/person/day from all sources, which is similar to the US (no data are available for New Zealand) (Fredholm *et al*., 1999). If this average figure of around 250 mg/person/day is taken to be the upper end of a 'low dose', this equates approx. to 3.5 mg/kg for a 70 kg human (approx. 10 mg/kg in rat), or 2-3 cups of coffee per day. This will result in a peak blood concentration range of between 0.75 - 6 mg/L or 3 - 30 μM (Fredholm *et al*., 1999). One cup of coffee per day, by contrast, would equate approx. to 83 mg or 1.2 mg/kg, resulting in a peak blood concentration range of 0.25 - 2 mg/L or 1 - 10 μM (Fredholm *et al*., 1999).

A2.1.2 Effects of caffeine at low doses

The effects of caffeine at specific dose levels and concentrations has been tabulated and summarised (Appendix 1 and 2).

Caffeine, even at ‘low’ doses of dietary consumption (80 mg/day in adults), generally produces measurable pharmacological effects. However, it must be acknowledged that current knowledge of the effects of caffeine is based almost entirely on the study of adults and children under one year (clinical treatment of neonatal apnoea). At low doses caffeine can produce behavioural responses in subjects, namely, self-reporting of a ‘liking’ for coffee was increased at doses of 25mg/cup (Griffiths *et al*, 1986). Following lengthy training some subjects also demonstrate an ability to discriminate caffeine at doses as low as 32 mg and in one individual as little as 18mg (Silverman *et al*, 1992).

Low doses of caffeine (ie., 20-200 mg) have generally been associated with effects on mood, such as feelings of increased energy, imagination, efficiency, self-confidence, alertness, motivation and concentration (Griffiths *et al*., 1990; Silverman *et al*., 1994; Griffiths and Mumford, 1995; Lane and Phillips-Bute, 1998; Robelin and Rogers, 1998; see Fredholm *et al*., 1999 for a review).

There seems little question that even low doses of caffeine, such as that contained in one cup of coffee, can increase the latency to, and reduce the quality of, sleep

(Landolt *et al*., 1995). Caffeine concentrations in the blood as low as 3 μM can affect the ability to sleep (see Fredholm *et al*., 1999 for a review). It has been reported that schoolchildren who consume more than 50 mg/day experience significantly greater wakefulness than controls receiving less than 10 mg/day (Goldstein and Wallace, 1997).

Many studies support the idea that caffeine, at low to moderate doses 60-400mg, as defined in section 2.1.1 reduces human reaction time on tasks like visual pattern recognition, delayed-matching to-sample and match-to-sample visual tasks (e.g, Durlach, 1998; Lane and Phillips-Bute, 1998; Hogervorst *et al*., 1998; Robelin and Rogers, 1998; Ruijter *et al*., 1999; Kenemans and Verbaten, 1998; Bryant *et al*., 1998; Kenemans *et al*., 1999; Rees *et al*., 1999; Marsden and Leach, 2000). Perhaps the best demonstration of this effect was a study by Durlach (1998), in which only 60 mg caffeine was shown to significantly reduce reaction time on several recognition tasks. However, the effect of caffeine in such tasks seems to be in speeding up performance rather than any enhancement of memory itself (Smith et al., 1999: Herz, 1999). Some authors even question whether performance is enhanced and suggest that any improvement is due to relief of withdrawal symptoms (e.g, James, 1998; Rogers and Dernoncourt, 1998).

Although occasional claims appear in the literature regarding certain persons having peculiar or idiosyncratic sensitivity to caffeine, such claims *generally* lack objective substantiation. The exceptions to this general rule are: acute effects of low doses of caffeine have been reliably observed (a) in persons with compromised liver function (Scott *et al*., 1988, 1989; Statland & Demas, 1980; Statland *et al*, 1976; Wahlländer *et al.*, 1983), and (b) in some individuals when caffeine is taken in combination with certain medications which inhibit caffeine metabolism (Tarrus *et al*, 1987; Jeppesen *et al*, 1996).

However, it is important to make a distinction between effects (eg on mood, the efficiency of mental performance and sleep) in relation to the amounts of caffeine that are normally consumed from food and drinks and the very different effects observed with excessive amounts or in very sensitive individuals. Unlike other areas of research (e.g. studies of health effects) most studies of the behavioural effects of caffeine have examined acute responses following a single dose. Less is known about effects of regular consumption although there is now enough data on this topic to draw tentative conclusions. In addition to studying effects of caffeine consumption the research has also considered possible changes in behaviour as a function of caffeine withdrawal.

Ideally, it would be valuable to have data which would enable dose-response and plasma concentration-response curves to be established for different effects (end-points). However, it appears that the relationship between dose and physiological response is continuous at low levels (although behavioural effects are increasingly subtle as dosage is reduced). Therefore, there is no evidence of a 'no effect' level.

A2.1.3 Summary of effects of caffeine at low doses

Overall, the majority of literature suggests that the effects listed below (points 1-6) may occur when individuals consume low to moderate (60-400mg/day) amounts of caffeine (eg by taking repeated low doses in the diet during the day). However, it

must be noted that the basis for the effects observed at low doses is a controversial topic and some literature reports (James, 1994a; 1998) suggest that caffeine merely removes negative effects associated with caffeine withdrawal (See under Term of Reference B) for a discussion of withdrawal effects).

(1) ***Caffeine increases alertness and reduces fatigue (as defined by measurable behavioural effects).*** This may be especially important in low arousal situations (*e.g*., working at night - Smith *et al*., 1993a; early morning - Smith *et al*., 1992; following administration of benzodiazepines - Johnson *et al*., 1990; when the person has a cold - Smith, 1994; and sleep loss - Bonnet *et al*., 1995).

(2) ***Caffeine improves performance on vigilance tasks and simple tasks which require sustained response.*** Again, these effects are often clearest when alertness is reduced although there is evidence that benefits may still occur when the person is unimpaired (Regina *et* al., 1974; Clubley *et al*., 1979, Lieberman, 1992). At low plasma concentrations caffeine increased psychomotor performance measures of attention in healthy elderly volunteers (Bryant, *et al*. 1998).

(3) ***Caffeine and more complex tasks.*** Effects on more complex tasks are difficult to assess and probably involve interactions between the caffeine and other variables which increase alertness (e.g. personality and time of day) (Revelle *et al*, 1987).

(4) ***Caffeine withdrawal effects on performance.*** In contrast to the effects of caffeine consumption, withdrawal of caffeine has few effects on performance. There is often an increase in negative mood following withdrawal of caffeine but such effects may largely reflect the expectancies of the volunteers and the failure to conduct "blind" studies (Rogers *et al*, 1995; Griffiths *et al*, 1986).

(5) ***Regular consumption of caffeine***. Some studies have suggested that regular consumption of caffeine can improve cognitive performance, ie, simple reaction times, choice reaction time, incidental verbal memory and visuo-spatial reasoning (Loke, 1988; Loke, 1989; Smith *et al.,* 1993b; Jarvis, 1993). This view is confirmed by other studies which suggest that non-consumers of caffeine have the worst performance (Jacobsen and Thurman-Lacey, 1992) especially when challenged with caffeine. There are exceptions which have shown high users to be impaired (Mitchell and Redman, 1992), although these effects are often restricted to the performance of specific tasks.

(6) ***Caffeine and effects on sleep***. Generally, subjects consume caffeine in a small dose range over the course of a day, with caffeine predominately consumed early in the day and intakes reducing later in the day followed by overnight abstinence. Additionally, adult subjects often reduce their caffeine intake according to its effect on their sleep patterns (see Fredholm *et al*., 1999 for a review).

A2.2 Effects of higher dosage

Some studies have demonstrated negative effects when very large amounts (>500 mg/day) of caffeine are given or sensitive groups (e.g. patients with anxiety disorders) studied (Lader and Bruce, 1986; Liebermann, 1992). In this context caffeine has been shown to increase anxiety and impair sleep. There is also some evidence that fine

motor control may be impaired, which may be plausibly related to the increase in anxiety.

High levels of caffeine intake have been associated with anxiety (Hughes, 1996) and caffeine has been shown to reduce the binding of benzodiazepines to the $GABA_A$ receptor at doses of greater than 20 mg/kg (see Fredholm *et al*., 1999 for a review). However, large population studies have failed to find a significant relationship between caffeine intake and anxiety disorders (e.g, Eaton and McLeod, 1984), possibly because people who suffer from anxiety may reduce their caffeine intake of their own volition (see Fredholm *et al*., 1999 for a review). In addition, anxiety in patients with anxiety disorders has not been demonstrated to be related to caffeine intake (e.g, Rihs *et al*., 1996). Unfavourable subjective and somatic effects and performance disruption have been observed at caffeine doses of 500 mg/day (Kaplan *et al*, 1997).

A2.3 Interpretation of effects

Data on effects in children

The literature relating specifically to effects of caffeine in children is inadequate to provide firm conclusions about the potential behavioural effects, effects of withdrawal and health effects. The general literature on caffeine reveals that it has been a long-standing controversial topic with little unanimous agreement among experts in the field.

Very few studies of caffeine have been undertaken in children older than one year or in adolescents. Nevertheless, there appear to be no *a priori* reasons for suspecting children and adolescents to be any more sensitive to caffeine at low doses than adults, although this cannot be discounted. On the basis of the metabolism and pharmacokinetic data above, it might be speculated that onset of withdrawal effects may be more rapid in children due to the fact that the caffeine $t_{½}$ appears to be correspondingly shortened in children (refer to section 1.2).

Basis of effects on mood

There is debate as to whether the positive effects of caffeine on mood are due to the intrinsic reinforcing properties of caffeine or the relief from withdrawal symptoms (e.g, James, 1998). Some authors even question whether performance is enhanced and suggest that any improvement is due to relief of withdrawal symptoms (e.g, James, 1998; Rogers and Dernoncourt, 1998).

This issue has not been resolved but some authors argue that caffeine has positive effects on mood even at doses too low to induce withdrawal symptoms (e.g, see Fredholm *et al*., 1999 for a review).

A3.0 Conclusions

A3.1 Caffeine Metabolism and Pharmacokinetics

Caffeine is readily absorbed from the gastro-intestinal tract and metabolised in the liver producing three primary bio-transformation products; namely paraxanthine, theobromine and theophylline. Once formed, these metabolites are subject to extensive metabolism.

Available data suggests that pathways of caffeine metabolism are similar in adults and children. The clearance of caffeine is up to 2-fold higher in prepubescent children than in non-smoking adults, and declines with sexual maturation. Caffeine $t_{½}$ appears to be correspondingly shortened in children. There is no evidence to suggest that the volume of distribution or plasma protein binding of caffeine differs between children and adults. The elimination of the primary caffeine metabolites PX and TP (and to some extent TB) would similarly be expected to be enhanced in children.

A3.2 Effects of low doses of caffeine in adults

Considerable individual variation exists in relation to caffeine-induced effects which makes the determination of a dose-response relationship problematical.

However, the available data suggests that at low doses of caffeine (20-200mg) positive associations (increased energy, alertness, motivation and concentration) are observed. In some subjects, there may also be increased performance (eg improved cognitive performance, reduced reaction times, improved performance on vigilance tasks and simple tasks requiring a sustained response). However, there is still debate as to whether the positive effects of low doses of caffeine on mood are due to the intrinsic reinforcing properties of caffeine or the relief from withdrawal symptoms. Some authors argue that caffeine has positive effects on mood even at doses too low to induce withdrawal symptoms.

Consumption of caffeine in adults at doses of >250 mg/day can elucidate negative effects such as excitability and anxiety. Animal experiments have suggested that at high doses caffeine can induce changes in brain neurotransmitters thus supporting a pharmacological basis for behavioural effects in humans.

A3.3 Effects of low doses of caffeine in children

The literature relating specifically to effects of caffeine in children is inadequate to provide firm conclusions about the effects of caffeine on behaviour, its potential to cause withdrawal symptoms or its potential to produce long term adverse health effects at different dose levels. Detailed study of the general literature on caffeine reveals that it has been a controversial topic. This means that any specific view of the above issues will not have unanimous agreement. Very few studies of caffeine have been conducted in children older than one year or in adolescents. Nevertheless, there are no *a priori* reasons for suspecting children and adolescents to be any more sensitive to caffeine at low doses than adults.

On the basis of the metabolism and pharmcokinetic data, it might be speculated that onset of withdrawal effects, if these occur, may be more rapid in children due to the fact that the caffeine $t_{½}$ appears to be correspondingly shortened in children.

A4.0 Overall conclusions

The overall conclusions are based on the available literature on caffeine detailed in the text and, in addition, studies cited in the appendices.

Several variables need to be considered when interpreting studies with caffeine. These include the pharmacokinetics (eg age and sex differences, pregnancy, liver disease, diet, smoking and concomitant drug therapy), the source of caffeine (eg caffeinated beverages such as coffee may have physiological effects related to other constituents), the study design, the population studied and the sample size.

It would be valuable to have data which would enable dose-response and plasma concentration-response curves to be established for different effects (end-points). However, it is likely that the relationship between dose and most physiological responses are continuous at low levels (although behavioural effects are increasingly subtle as dosage is reduced). A 'no effect' level has not been identified. It is likely that caffeine can cause effects dose levels lower than those specifically studied however the detection of effects at low dose levels is ultimately dependent on the sensitivity of indicators and tests employed.

Although larger controlled studies are required to confirm the dose-related effects of low-dose caffeine, the following conclusions can be drawn from the available data:

- There are reports of enhanced performance and mood effects at doses of 37.5mg (0.54 mg/kg bw/day in 70 kg adults);

- There are reports of increased anxiety levels in children at doses of 95mg (3 mg/kg bw/day in children aged 5-12 years with a mean bodyweight of 32kg) and at 210mg in adults (3 mg/kg bw/day in 70 kg adults; and

- Caffeine has been reported to reduce the ability to sleep at doses of 100mg (1.4 mg/kg bw/day in 70 kg adults) at bedtime.

In conclusion, in addressing term of reference A, the threshold dose for possible behavioural effects in children remains unclear and it is recognised that further studies are needed to elucidate the potential effects of caffeine in children at doses that may be ingested from dietary sources.

TERM OF REFERENCE B

The potential for an addictive effect of caffeine.

B1.0 Caffeine Dependence

Physiological ‘dependence', defined by the occurrence of withdrawal symptoms upon abstinence, has been demonstrated to develop following regular caffeine consumption.

B 1.1 Withdrawal Symptoms

The withdrawal symptoms usually include tiredness, weakness, headaches, nausea and flu-like feelings (see Fredholm *et al*., 1999 for a review). Even short periods of caffeine deprivation have been associated with decreased vigour, increased fatigue, increased sleepiness and yawning and lower blood pressure (Phillips-Bute and Lane, 1998) and unpleasant effects by the middle of the day (Lane, 1997).

The scale of reporting of symptoms varies considerably from study to study (20% of sample, Fenelly *et al*. 1991; 50% Silverman *et al*.., 1992; 100% Naismith *et al*. 1970). Dews et al. (1999) examined the frequency of caffeine withdrawal symptoms in a sample of over 11,000 persons. 11% of the caffeine consumers reported symptoms upon stopping caffeine. Of the regular caffeine consumers only 0.9% of males and 5.5% of females reported symptoms significant enough to interfere with normal activities when they abruptly stopped caffeine. A sub-sample of participants who reported caffeine withdrawal in the past were also studied under a double-blind caffeine/caffeine withdrawal manipulation. Most did not show withdrawal symptoms in the double blind study (Dews *et al*, 1999).

There seems to be some consensus that the severity of the withdrawal syndrome is greater in heavy users than light users (see Fredholm *et al*., 1999 for a review); however, some studies have found withdrawal symptoms even in subjects with a daily caffeine intake as low as 129 mg (e.g, Strain *et al*., 1994).

If a mild withdrawal syndrome did develop following abstinence from regular low dose caffeine use, this might not be significant provided that the continued use of caffeine due to dependence did not have adverse effects on health. The issue of dependence for low doses also relates to the interpretation of data purportedly demonstrating that caffeine improves mood and psychomotor performance. If such improvements are due simply to the relief of withdrawal symptoms as some authors contend (e.g, James, 1994a), then dependence must develop even for low doses of caffeine. However, others argue that caffeine withdrawal does not consistently lead to a decrease in performance (e.g, Rogers et al., 1995) and that it appears to enhance performance even in the absence of withdrawal symptoms (e.g, very low doses) (Rogers *et al*., 1995; Warburton, 1995; see Fredholm *et al*., 1999 for a review).

B2.0 Summary of effects

In pharmacology, physical dependence is defined by physiological and behavioural disruptions (ie withdrawal syndrome) upon termination of drug administration.

Therefore, although it is recognised that ingestion of caffeine at low doses may lead to some positive effects it may also reflect an attempt to avoid a negative response (ie to avoid withdrawal symptoms). The withdrawal syndrome that accompanies abstinence following regular habitual use is therefore the primary expression of physical dependence.

As determined in Term of Reference A adverse effects may be experienced in adults following consumption of caffeine at doses >250 mg/kg. It is also recognised that a reduction in intake of caffeine or total abstinence from caffeine can lead to withdrawal type symptoms. Headache and fatigue are the most frequent reported withdrawal symptoms, with a variety of symptoms occurring at lower frequency (increased work difficulty, impaired psychomotor performance, anxiety and nausea/vomiting).

Other studies have suggested that subjective perceptions and expectancies play a major role in the effects of caffeine withdrawal (Smith, 1996; Rubin & Smith, 1999; Dews et al., 1999) a view that contrasts strongly with the notion that a significant proportion of caffeine consumers are physically dependent upon caffeine.

B3.0 Interpretation of effects

Discussion under this term of reference could have led to irreconcilable differences over interpretation, as the word "addictive" is value laden in ordinary discourse. (Heller T, Gott M and Jeffery C (1987). *Drug Use and Misuse: A Reader*. Page 40.)

The International Classification of Diseases, 10th revision (ICD 10; 1998) recognises (under the group of diagnoses headed "Mental and behavioural disorders due to psychoactive substance use") the disorder F15: "Mental and behavioural disorders due to other stimulants, including caffeine". Further descriptors, some of which could be used to describe disorders occurring with caffeine use, are available within the classification scheme: .0 Acute intoxication; .1 Harmful use; .2 Dependence syndrome; .3 Withdrawal state; .4 Withdrawal state with delirium; .5 Psychotic disorder; .6 Amnesic syndrome; .7 Residual and late-onset psychotic disorder; .8 Other mental and behavioural disorders; and .9 Unspecified mental and behavioural disorder.

"Dependence syndrome" is defined as follows:

- A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.

- The dependence syndrome may be present for a specific psychoactive substance (eg tobacco, alcohol, or diazepam), for a class of substances (eg opioid drugs), or for a wider range of pharmacologically different psychoactive substances.

- Chronic alcoholism
  Dipsomania

Drug addiction

The last example places the concept "addiction" within the ICD classification.

Clearly, physiological dependence can occur with caffeine use. (Note that the term "physiological dependence" corresponds to "withdrawal state" in ICD 10, and physiological dependence on caffeine would be classified as F15.3) But the evidence available does not justify a finding that the disorder "dependence syndrome", as defined by ICD 10, results from caffeine use.

Some recent studies support the view that caffeine has different central nervous system effects compared to addictive drugs (Daly and Fredholm, 1998; Nehlig, 1999).

B4.0 Overall conclusion

It is concluded that caffeine at doses typically consumed in the diet may lead to withdrawal effects and some physical dependence in adults. The prevalence of such effects has been variable, as has the interpretation but in most individuals they are mild in intensity. Further research will be required at doses typically consumed in the diet to examine whether similar physical dependency occurs in children.

Term of Reference C

Identification of any other hazards in children (e.g. long-term health effects) resulting from consumption of caffeine at low doses.

Research on caffeine has focused on the potential for effects associated with dependence and withdrawal, effects on reproduction, genotoxicity, carcinogenicity, cardiovascular effects and effects on behavioural and cognitive function in children and adults. A large amount of research has been undertaken and a number of reviews are available (Stavric, 1992; Nehlig and Debry, 1994 a and b; Lamarine, 1994; D' Ambrosio, 1994; Binns, 1995; and Barone and Roberts, 1996; James, 1991; 1997b). Some of the more prominent general health effects of caffeine are discussed below.

C1.0 General health effects of caffeine

C1.1 Effects on the foetus, pregnancy and reproductive parameters

Caffeine use during pregnancy is widespread with the majority of newborn infants having measurable levels of caffeine in their blood (which could only have been received from the mother). There is limited evidence that caffeine consumed during pregnancy may reduce birth weight and increase the risk of spontaneous abortion (James, 1997b; Chapter 7; pp 116-124), particularly at doses >300 mg/day (Hinds *et al* 1996). For example one study reported a reduction in birth weight amongst mothers consuming over 71 mg/day (Vlajinac *et al*, 1997). Confounding by other factors such as maternal smoking, alcohol or parity provide an alternative explanation for the findings. Some recent studies have found no relationship with either lower birth weights (Santos *et al*, 1998) or increased risk of spontaneous abortion (Fenster *et al*, 1997).

Effects on cardiac parameters (eg decreases in maternal pulses and foetal heart rate) have been reported in pregnant women taking doses of 90 mg (1.3 mg/kg bw/day in 70 kg adults) (Miller *et al*, 1994). In addition, evidence has been presented suggesting that newborns may sometimes experience distress due to caffeine withdrawal associated with intrauterine exposure to caffeine (McGowan *et al*, 1988; Thomas, 1988; In: James, 1997b; pp127-128).

C1.2 Interactions with other drugs

Considering the near-universal use of caffeine, it is inevitable that its use will often coincide with usage of other drugs, taken for either recreational or therapeutic purposes. For example, caffeine has been shown to reduce the effectiveness of benzodiazepines (File *et al*.,1982; Loke *et al.*,1985; Mattila *et al*.,1982; Roache & Griffiths, 1987), interact with benzodiazepines at the receptor level (Boulenger *et al.*,1982; Holloway *et al*.,1985; Marangos, Martino *et al*.,1981; Phillis *et al*.,1983) and to cause nausea and vomiting in some people when ingested concurrently with certain broad spectrum antibiotics (Borcherding *et al.,*1996). Caffeine may enhance the effect of certain analgesics (Laska *et al*, 1994).

C1.3 Effects on calcium

Because caffeine increases the rate of elimination of calcium from the body, it has been suggested that life-long use of the drug may contribute to the development of osteoporosis, particularly in women. Present findings are inconclusive with further study needed (James, 1997b; p32).

C2.0 Cardiovascular effects of caffeine

C2.1 Acute effects of caffeine on blood pressure and tolerance

Single high doses of caffeine have been reported to produce tachycardia and acute increases in blood pressure (James, 1991; James, 1994b; Rachima-Maoz, et al.; 1998; Daniels et al., 1998; Smith et al., 1999; Fredholm et al., 1999). At lower doses of caffeine (250 mg) significant increases in systolic and diastolic blood pressure in older (58 years) hypertensive patients have been found (Rachima-Maoz et al., 1998). However, the effect of low doses of caffeine has not been accurately measured, although a small increase in diastolic pressure has been detected after single doses (140 mg) of caffeine in normal volunteers (Benowitz et al, 1995).

Although tolerance to these effects of caffeine on blood pressure has been reported (e.g, Ammon, 1991; Shi et al., 1993) some studies suggest that such tolerance is incomplete (Hofer and Battig, 1993). For this reason the results of longer-term studies assessing the relationship between caffeine consumption and blood pressure are particularly relevant.

C2.2 Longer term effects of caffeine on blood pressure

The longer term effects of caffeine on blood pressure have been studied in several large epidemiological studies conducted amongst consumers of different levels of coffee and tea. # Five such studies have been published since 1990 and their results are summarised below. It should be noted that observational studies involving tea and/or coffee consumption are prone to confounding by other factors related to caffeine intake, in particular alcohol intake.

(i) Wakabayashi and co-workers (1998) reported a significant inverse relationship between habitual coffee consumption and blood pressure (BP) in 3336 adult males aged 48-56 years with and without adjustment for alcohol use, cigarette smoking, body mass index, glucose tolerance and green tea intake. Green tea, a major source of caffeine intake in Japanese was not related to blood pressure. The adjusted mean differences in blood pressure per cup of coffee consumed per day were –0.6 mmHg (95% CI –0.9 to –0.3, p=0.0001) for systolic BP and –0.4mm Hg (95% CI –0.5 to -0.2, p=0.0002) in diastolic BP. Habitual coffee drinkers had lower BP than non-drinkers at any levels of alcohol use, cigarette smoking, obesity and glucose intolerance.

Note added in printing: the implication that the five studies summarised were all those published since 1990 is incorrect. These studies are a selection of the more recent studies believed to be representative. A similar comment applies to section C2.3.

(ii) Stamler and co-workers (1996, 1997) looked at dietary variables for 1-6 years and relations to systolic and diastolic BP for men in the intervention and usual care in the Multiple Risk Factor Intervention Trial. Caffeine intake was inversely related to systolic and diastolic blood pressure.

(iii) Palatini and co-workers (1996) studied the relationship between coffee consumption and plasma renin activity and office and 24 hour blood pressure in the multicentre HARVEST trial in Italy of 351 untreated borderline to mild hypertensive men (mean age 22.7+0.47 years). They reported no difference for office and whole-day BP, heart rate and urinary catecholamines with coffee intake. In a multiple linear regression model supine plasma renin activity was negatively correlated with age, coffee consumption and physical activity habits but the clinical significance of this finding is unclear.

(iv) Narkiewicz and co-workers (1995) investigated the effect of moderate smoking and coffee consumption on blood pressure using a case-control study with 887 patients from the multicentre Hypertension Ambulatory Venetia Study. In men with mild hypertension daytime systolic BP was significantly higher in smokers than non-smokers and coffee drinkers than non-drinkers. Analysis revealed a significant interaction between smoking status and coffee consumption. Daytime systolic BP in smokers who drank >4 cups/day coffee was 6.0mm higher than non-smokers who abstained from coffee. Office BP was lower in smokers than non-smokers and was similar in coffee drinkers and non-drinkers. Similar effects were seen in women.

(v) Lewis and co-workers (1993) examined the associations of caffeine and caffeinated beverage intake with blood pressure and lipoproteins in a cohort of 5,115 black and white men and women 18-30 years. Caffeine and beverages intake were not consistently associated with blood pressure or lipoproteins (cholesterol, triglycerides, high-density lipoprotein cholesterol) after controlling for confounders.

In summary, two of the five epidemiological studies revealed an inverse relationship between caffeine intake and blood pressure, two revealed no relationship and one yielded a positive relationship. The latter was a case control study which is widely regarded as the least reliable epidemiological methodology for ascertaining a relationship such as this.

C2.3 Epidemiological Studies of the Effect of Caffeine on Cardiovascular Disease

Epidemiological studies linking caffeine intake to either myocardial infarction or stroke have also focused on either coffee and or tea as sources of caffeine. Potential confounders in these studies include alcohol use, physical activity, smoking, serum lipids, body mass index, diabetes and social class since all of these may vary with caffeine intake . The findings from these studies are summarised below.

(i) Weinmann and coworkers (1997) undertook a population based case (362)-control (581) study to evaluate the association between caffeine intake (coffee, tea, cola) and primary cardiac arrest. After adjusting for cigarette smoking and other risk factors there was little association between <687mg/day caffeine (ie 5 cups coffee) and primary cardiac arrest. High caffeine consumption (>687mg/day) was associated with

a small increase in primary cardiac arrest (OR[1]=1.44, 95%CI=0.82-2.53) this increased risk was restricted to never-smokers (OR3.2, 95%CI=1.3-8.1).

(ii) Sesso and coworkers (1999) in a study of 340 cases of myocardial infarction and aged matched community controls demonstrated an odds ratio (OR) of 0.84 for drinking >4 cups coffee/day versus <1cup/week (95% Confidence Interval (CI) 0.49-1.42) after adjustment for coronary risk factors. The odds ratio for >1 cup/day decaffeinated coffee versus non-drinkers was 1.25 (95% CI 0.76-2.04). Tea was associated with a lower risk of myocardial infarction, odds ratio for >1 cup/day of tea versus non-drinkers was 0.56 (95% CI 0.35-0.90).

(iii) Palmer and co-workers (1995) investigated the relationship between caffeine and nonfatal myocardial infarction in a case -control study of 858 Massachusetts women with first infarcts and 858 community controls. Multiple logistic analysis demonstrated an increased risk of myocardial infarction with increasing number of cups per day of any type of coffee (p=0.002) and caffeine containing coffee (P=0.0004). The Relative Risk (RR)[2] for 5-6 cups per day caffeine containing coffee relative to <1cup/day were 1.4 (95% CI 0.8-2.5), 7-9 cups/day RR= 2.1 (95%CI 0.9-4.9) and >10 cups/day RR=2.5 (95%Ci 1.0-6.5). No increase was observed for <5cups/day. The positive association with heavy coffee drinking was present for nonsmokers and smokers.

(iv) Gyntelberg and co-workers (1995) undertook a prospective study of coffee consumption and ischaemic heart disease in 2975 men (53-74 years) without cardiovascular disease at baseline from the Copenhagen Male Study. 184 men had a first ischaemic heart disease event. There was no significant difference between those consuming 1-4, 5-8 or >9 cups/day after controlling for confounders (p-value of trend test=0.14). The crude incidence rates were 6.8%, 6.7% and 4.6% and adjusted rates were 6.8%, 6.7% and 4% respectively. Coffee consumption was significantly ($p<0.05$) inversely correlated with serum selenium and positively or negatively associated with smoking, alcohol use, serum triglycerides, serum cholesterol, blood pressure, social class and body mass index (BMI). The association of coffee consumption and ischaemic heart disease is conditioned by known risk factors.

(v) Hakim and co-workers (1998) examined coffee intake and stroke in a cohort of 499 hypertensive men (55-68 years) enrolled in the Honolulu Heart Program who were followed for over 25 years. 76 men developed a stroke. After age adjustment risk of thrombo-embolic stroke increased significantly with coffee consumption ($p<0.002$) and after adjusting for other factors the Relative Risk (RR)[3] was 2.1 (95% CI 1.2-3.7) for men consuming 3 cups/day compared to non-drinkers. There was no relationship for haemorrhagic stroke. Therefore this study showed a positive association with increased risk of thrombo-embolic stroke in hypertensive men in older middle-age.

In summary, there are five major epidemiological studies examining the relationship between caffeine intake and cardiovascular disease and stroke published since 1990. Four were case-control studies, one of which revealed a weakly protective effect,

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[1] The ratio of the probability of occurrence of an event to that of non-occurrence.
[2] The ratio of the risk of disease or death among the exposed to the risk among the unexposed.

while three revealed a weak but graded relationship between coffee intake and myocardial infarction or stroke. The single cohort study found no relationship. The results are therefore inconclusive but suggest that the relationship if present is likely to be weak and clinically unimportant.

In addition, a 1994 review of caffeine and associated health effects concluded that the relationship between caffeine consumption and various diseases such as cardiovascular disease and cancer remains equivocal (Lamarine, 1994). Chou and Benowitz (1994) have concluded that the published literature provides little evidence that coffee and/or caffeine in typical dosages increases the risk of infarction, sudden death or arrhythmias.

C2.4 Reviews of Clinical and Epidemiological Studies

In a review Nurminen (1999) concluded that acute intakes of coffee and caffeine increase blood pressure with the pressor response strongest in hypertensive subjects. Repeated caffeine administration showed either a persistent pressor effect in some studies and no increase in blood pressure in others (Nurminen *et al*, 1999).

A meta-analysis of 11 of 36 'multidose' studies reported an increase of 2.4mm Hg in systolic blood pressure and 1.2mm Hg in diastolic blood pressure with coffee intake (median dose of coffee was 5 cups/day and trials lasting for >24 hours) compared to controls (Jee *et al*, 1999). The number of subjects in these trials ranged from 8 to 99 (median 45) and the study duration was from 14 to 79 days (median 56 days).

Multiple linear regression analysis identified an independent positive relationship between cups of coffee consumed and subsequent change in systolic blood pressure, independent of age of study participants and study design characteristics. The effect of coffee on systolic and diastolic blood pressure was greater in trials with younger participants. Meta analyses of 8 case-control and 15 cohort studies were pooled and analysed by study design, sex, coronary heart disease endpoints, smoking habit and period of study. The pooled case-control odds ratio was 1.63 (95% CI 1.5-1.78) and the pooled cohort study gave a relative risk of 1.05 (95%CI 0.99-1.12) for drinking 5 cups/day of coffee versus none (Kawachi et al, 1994). It should be noted that meta-analyses of observational studies such as these is controversial and potentially unreliable

Another review of the effects of caffeine on blood pressure and heart rate concluded that the results from epidemiological studies were inconclusive whereas clinical trials have generally found that caffeine produces acute rises in systolic and diastolic blood pressure that are additive to stress induced changes (Green *et al*, 1996).

Overall the relationship between chronic caffeine intake and blood pressure has not been established with certainty but is unlikely to be clinically significant. Whereas the results from small clinical trials have demonstrated small increases in blood pressure following acute caffeine ingestion the preponderance of data has not indicated any longer term relationship. This would be compatible with the development of a substantial degree of tolerance to the hypertensive effects of caffeine with regular consumption.

C2.5 New Zealand Heart Foundation Report

An unpublished Report (Coffee and Caffeine: A Background Paper 2000) from the New Zealand Heart Foundation reviewed the association between caffeine in coffee and cardiovascular disease (CVD) and concluded the following:

- The method of brewing coffee will often be the determining factor when describing its association with CVD risk factors.

- The consumption of boiled or plunger coffee raises total cholesterol primarily through an increase in blood low density lipoprotein-cholesterol. This is a dose-dependent relationship.

- Two lipid-containing substances, cafestol and kahweol, have been implicated as the components in coffee responsible for its hypercholesterolaemic effects.

- Cessation of caffeine consumption or a change to decaffeinated coffee in habitual caffeine consumers may lower ambulatory blood pressure levels among normotensive individuals. The evidence is less clear for borderline hypertensive individuals, and a recommendation cannot be made until further Randomised Control Trials (RCT's) are conducted within this high-risk population group.

- The trials examining caffeine and arrhythmias are conflicting. Until larger RCT's are conducted, a conservative approach would be to recommend that people with arrhythmias limit their consumption of caffeine-containing beverages.

C3.0 Interpretation of effects

Caffeine has been studied as a potential associate with a range of health problems. In some instances apparent health effects of caffeine is possibly explained by confounding through factors linked to caffeine intake, particularly smoking status and alcohol intake. Other health effects have been anticipated by the extrapolation of studies of acute physiological effects of caffeine (e.g. effects on sleep or cardiovascular functioning) but the associations between these and long-term health are still unclear. Further research is still required on caffeine consumption in childhood and later health problems and the existing literature does little to clarify this issue. There is virtually no information about whether children face any additional risks to those listed above. It should be noted however that a pattern of consumption of caffeine may be established early in life.

Although specifying 'hazards in children', Term of Reference C cites 'long-term health effects' as the particular example. By definition, this would include consideration of, health effects arising post-childhood which might be associated with caffeine use during childhood. While there has been very little study of caffeine-induced hazards in children older than one year, post-childhood hazards have been extensively studied (albeit not always with consistent findings).

C4.0 Overall conclusions

A link between caffeine contributing to cardiovascular disease has not been established. The published literature provides little evidence that chronic caffeine intake in typical dosages consumed in the diet contributes to hypertensive disease.

If it is assumed that caffeine use in childhood lays the foundations for life-long use, there may be some grounds for considering that the consumption of high intakes of caffeine-containing substances by children could be undesirable. However at this stage it is not possible to conclude that patterns of caffeine consumption established early in life can contribute to negative long-term health outcomes in children or adults.

REFERENCES

Al'Absi,M., Lovallo, W.R., McKey, B. et al. (1998) Hypothalamic-pituitary-adrenocortical responses to psychological stress and caffeine in men at high and low risk for hypertension. *Psychosomatic Medicine.* **60**: 521-527.

Ammon, H.P. (1991) Biochemical mechanisms of caffeine tolerance. *Archives of Pharmacology.* **324**: 261-267.

Aranda JV, Collinge JM, Zinman R, Watters G. (1979) Maturation of caffeine elimination in infancy. *Arch Dis Child*; **54**: 946-949.

Barone JJ and Roberts HR. (1996) Caffeine consumption. *Fd. Chem. Toxic***.**, **34**, 119-129.

Bennett, H.J. and Semba, K. (1998) Immunohistochemical localization of caffeine-induced c-Fos protein expression in the rat brain. *Journal of Comparative Neurology.* **401**: 89-108.

Benowitz, NL. *et al* (1995) Sympathomimetic effects of paraxanthine and caffeine in humans. *Clin Pharmacol Ther*; **58**:684-91.

Birkett DJ and Miners JO. (2000) Methylxanthines. In *Metabolic Drug Interactions*. eds Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum ME, New York: Lippincott Williams & Wilkins, 2000: chapter 35.

Binns NM. (1995) Caffeine. *BNF-Nutrition Bulletin*, **20** (Suppl.), 278-285.

Blanchard J and Sawers SJA. (1983) Comparative pharmacokinetics of caffeine in young and elderly men. *J Pharmacokinet Biopharm*; **11:** 109-126.

Bonnet M. H., Gomez S., Wirth O., and Arand D. L. (1995) The use of caffeine versus prophylactic naps in sustained performance. *Sleep* **18,** 97-104.

Boulenger JP, Patel J and Marangos PJ (1982) Effects of caffeine and theophylline on adenosine and benzodiazepine receptors in human brain. *Neuroscience Letters*, **30**, 161-166. In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Borcherding SM, Stevens R, Nicholas RA et al (1996) Quinolones: a practical review of clinical uses, dosing considerations and drug interactions. *Journal of Family Practice*, **42**, In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Bryant, C.A., Farmer, A., Tiplady, B. *et al.* (1998) Psychomotor performance: investigating the dose-response relationship for caffeine and theophylline in elderly volunteers. *European Journal of Clinical Pharmacology.* **54**: 309-313.

Callahan MM, Robertson RS, Branfman AR, McComish MF and Yesair DW (1983) Comparison of caffeine metabolism in three nonsmoking populations after oral administration of radiolabeled caffeine. *Drug Metab Dispos*; **11**: 211-217.

Campbell ME, Spielberg SP and Kalow W (1987) A urinary metabolite ratio that reflects systemic caffeine clearance. *Clin Pharmacol Ther*; **42**: 157-165.

Carrier O, Pons G, Rey E, Richard M, Moran C, Badoual J and Olive G (1988) Maturation of caffeine metabolic pathways in infancy. *Clin Pharmacol Ther*; **44**: 145-151.

Clubley M., Bye C. E., Henson T. A., Peck A. W. and Riddington C. J. (1979) Effects of caffeine and cyclizine alone and in combination on human performance, subjective effects and EEG activity. *British Journal of Clinical Pharmacology* **7,** 157-163.

D'Ambrosio SM. (1994) Evaluation of genotoxicity data on caffeine. *Regulatory Toxicology and Pharmacology***,** 19, 243-281.

Daly JW and Fredholm BB (1998) Caffeine-an atypical drug of dependence. *Drug Alcohol Dependenc*e, **51**, 199-206.

Daniels, J.W., Mole, P.A., Shaffrath, J.D. and Stebbins, C.L. (1998) Effects of caffeine on blood pressure, heart rate and forearm blood flow during dynamic exercise. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology.* **85**: 154-159.

Denaro CP, Brown CR, Wilson M, Jacob P and Benowitz NL. (1990) Dose-dependency of caffeine metabolism with repeated dosing. *Clin Pharmacol Ther*; **48**: 277-285.

Dews,P.B, Curtis,G.L, Hanford,K.J and O'Brien,C.P (1999*)* The frequency of caffeine withdrawal in a population-based survey and in a controlled blinded pilot experiment. *Journal of Clinical Pharmacology*, **39**: 1221-1232

Durlach, P.J. (1998) The effects of a low dose of caffeine on cognitive performance. *Psychopharmacology*. **140**: 116-119.

Eaton, W.W. and McLeod, J. (1984) Consumption of coffee or tea and symptoms of anxiety. *American Journal of Public Health.* **74**: 66-68.

Fenelly M, Galletly DC and Purdie GI (1991) Is caffeine withdrawal the mechanism of postoperative headache? *Anesthesia and Analgesia*, **72**: 449-453.

Fenster L, Hubbard AE, Swan SH et al (1997) Caffeinated beverages, decaffeinated coffee, and spontaneous abortion. *Epidemiology*, **8**: 515-523).

File SE, Bond AJ and Lister RG (1982) Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. *Journal of Clinical Psychopharmacology*, **2**, 102-106. In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Fredholm, B.B., Arslan, G., Kull, B. and Svenningsson, P. (1998) Locating the neuronal targets for caffeine. *Drug Development Research.* **45**: 324-328.

Fredholm, B.B., Battig, K., Holman, J., Nehlig, A. and Zvartau, E.E. (1999) Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews.* **51**: 83-133.

Gates S and Miners JO. (1999) Cytochrome P450 isoform selectivity in human hepatic theobromine metabolism. *Br J Clin Pharmacol*; **47**: 299-305.

Goldstein, A. & Kalant,H. (1990) Drug policy: Striking the right balance. *Science*, **249**, 1513.

Goldstein, A. and Wallace, M.E. (1997) Caffeine dependence in schoolchildren? *Experimental and Clinical Psychopharmacology. **5**: 388-392.*

Griffiths R. R., Bigelow G. E. and Liebson I. A. (1986) Human coffee drinking. Reinforcing and physical dependence producing effects. *Journal of Pharmacology and Experimental Therapeutics* **239,** 416-425.

Griffiths, R.R., Evans, S.M., Heishman, S.J., Preston, K.L., Sannerud, C.A., Wolf, B. and Woodson, P.P. (1990) Low-dose caffeine administration in humans. *Journal of Pharmacology and Experimental Therapeutics.* **252**: 970-978.

Griffiths, R.R. and Mumford, G.K. (1995) Caffeine - A drug of abuse? In F.E. Bloom and D.J. Kupler (Eds.) *Psychopharmacology: The Fourth Generation of Progress.* Raven Press, New York, pp. 1699-1713.

Grygiel JJ and Birkett DJ. (1980) Effect of age on patterns of theophylline metabolism. *Clin Pharmacol Ther*; **28**: 456-462.

Harlan, R.E. and Garcia, M.M. (1998) Drugs of abuse and immediate early genes in the forebrain. *Molecular Neurobiology.* **16**: 221-267.

Heishman,S.J. and Hemmingfield, J.E. (1999) Is caffeine a drug of dependence? Criteria and comparisons. In: Caffeine and Behaviour: Current views and research trends. B.S. and U. Gupta (eds). CRC Press : Washington. pp.137-150.

Herz, R.S. (1999) Caffeine effects on mood and memory. *Behaviour Research and Therapy.* **37**: 869-879.

Hinds T, West WL, Knight EM and Harland BF (1996). The effect of caffeine on pregnancy outcome variables, Nutrition Reviews, 54, 203-207.

Hofer, I. and Battig, K. (1993) Coffee consumption, blood pressure tonus and reactivity to physical challenge in 338 women. *Pharmacology, Biochemistry and Behavior.* **44**: 573-576.

Hogervorst, E., Riedel, W.J., Schmitt, J.A.J. and Jolles, J. (1998) Caffeine improves

memory performance during distraction in middle-aged, but not young or old subjects. *Human Psychopharmacology*. **13**: 277-284.

Holoway FA, Modrow HE and Michaelis RC (1985) Methylzanthine discrimination in the rat: possible benzodiazepine and adenosine mechanisms. *Pharmacology, Biochemistry and behaviour*, **22**: 815-824. In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Hughes, R.N. (1996) Drugs which induce anxiety: Caffeine. *New Zealand Journal of Psychology.* **25**: 36-42.

Jacobson B. H. and Thurman-Lacey, S. R. (1992) Effect of caffeine on motor performance by caffeine-naive and -familiar subjects. *Perceptual and Motor Skills* **74,** 151-157.

James, J.E. (1991) *Caffeine and Health.* Academic Press, London. pp. 1-432.

James J. E. (1994a) Does caffeine enhance or merely restore degraded psychomotor performance? *Neuropsychobiology* **30,** 124-125.

James J. E. (1994b) Chronic effects of habitual caffeine consumption on laboratory and ambulatory blood pressure levels. *Journal of Cardiovascular Risk*, **1**, 159-164.

James J. E. (1997a) Is habitual caffeine use a preventable cardiovascular risk factor. *Lancet*, **349**, 279-281.

James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

James J. E. (1998) Acute and chronic effects of caffeine on performance, mood, headache and sleep. *Neuropsychobiology* **38**, 32-41.

Jarvis MJ. (1993) Does caffeine intake enhance absolute levels of cognitive performance? *Psychopharmacology*, **110**, 45-52.

Jeppesen U, Loft S, Poulsen HE and Brsen K (1996*)* A fluvoxamine-caffeine interaction study. *Pharmacogenetics*, **6**, 213-222.

Johnson L. C., Spinweber G. L. and Gomez S. Z. (1990) Benzodiazepines and caffeine: Effect on daytime sleepiness, performance, and mood. *Psychopharmacology* **101,** 160-167.

Kaplan, G.B., Greenblatt, D.J., Ehrenberg, B.L., Goddard, J.E., Cotreau, M.M., Harmatz, J.S. and Shader, R.I. (1997) Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. *Journal of Clinical Pharmacology.* **37**: 693-703.

Kenemans, J.L., Wieleman, J.S.T., Zeegers, M. and Verbaten, M.N. (1999) Caffeine and stroop interference. *Pharmacology, Biochemistry and Behavior.* **63**: 589-598.

Kenemans, J.L. and Verbaten, M.N. (1998) Caffeine and visuo-spatial attention. *Psychopharmacology.* **135**: 353-360.

Lader M and Bruce M. (1986) States of anxiety and their induction by drugs. *British Journal of Clinical pharmacology*, **22**, 252-261.

Lamarine RJ. (1994) Selected health and behavioural effects related to caffeine. *Journal of Community Health*, 19, 449-466.

Lambert GH, Schoeller DA, Kotake AN, Flores C and Hay D. (1986) The effect of age, gender and sexual maturation on the caffeine breath test. *Dev Pharmacol Ther*; **9**: 375-388.

Landolt, H.P., Dijk, D.J., Gaus, S.E. and Borbely, A.A. (1995) Caffeine reduces low-frequency delta activity in human sleep EEG. *Neuropsychopharmacology.* **12**: 229-238.

Lane JD. (1997) Effects of brief caffeinated-beverage deprivation on mood, symptoms, and psychomotor performance. *Pharmacol Biochem Behav*; **58**:203-8.

Landolt HP et al. (1995) Caffeine intake (200mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res*; 675:67-74

Lane, J.D. and Phillips-Bute, B.G. (1998) Caffeine deprivation affects vigilance performance and mood. *Physiology and Behavior.* **65**: 171-175.

Laska E.M, Sunshine A, Mueller F *et al* (1994) Caffeine as an analgesic adjuvant. *Journal of the American Medical Association*, **251**: 1711-18.

Ledent, C., Vaugeois, J.M., Schiffmann, S.N. *et al.* (1997) Aggressiveness, hypoalgesia and high blood pressure in mice lacking the adenosine A_{2A} receptor. *Nature.* **388**: 674-678.

Lelo A, Miners JO, Robson RA and Birkett DJ. (1986a) Quantitative assessment of caffeine partial clearances in man. *Br J Clin Pharmacol*; **22**: 183-186.

Lelo A, Birkett DJ, Robson RA and Miners JO. (1986b) Comparative pharmacokinetics of caffeine and its primary demethylated metabolites paraxanthine, theobromine and theophylline in man. *Br J Clin Pharmacol*; **22**: 177-182.

Lelo A, Kjellen G, Birkett DJ and Miners JO. (1989) Paraxanthine metabolism in humans: determination of metabolic partial clearances and effects of allopurinol and cimetidine. *J Pharmacol Exp Ther*; **248**: 315-319.

Lieberman H. R. (1992) Caffeine. In *Handbook of Human Performance.* Edited by A. P. Smith and D. M. Jones. Vol. 2, pp. 49-72. Academic Press, London.

Loke W. H. (1988) Effects of caffeine on mood and memory. *Physiology and Behavior* **44,** 367-372.

Loke W. H. (1989) Effects of caffeine on task difficulty. *Psychologica-Belgica* **29,** 51-62.

Loke WH, Hinrichs JV and Ghoneim MM (1985) Caffeine and diazepam: separate and

combined effects on mood, memory and psychomotor performance. *Psychopharmacology*, **87**: 344-350. In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Lovallo WR *et al.* (1996) Stress-like adenocorticotropin responses to caffeine in young healthy men. *Pharmacol, Biochem Behav*; **55**:365-9.

Marangos PJ, Martino AM et al (1981) The benzodiazepines and inosine antagonise caffeine-induced seizures. *Psychopharmacology*, **72**: 269-273. In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Marsden, G. and Leach, J. (2000) Effects of alcohol and caffeine on maritime navigational skills. Ergonomics. **43**: 17-26.

Mattila ME, Mattila MJ and Nuotto E (1992) Caffeine moderately antagonises the effects of triazolom and zopiclone on the psychomotor performance of healthy subjects. *Pharmacology and Toxiciology*, **70**: 286-289. In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

McGowan JD, Altman, RE and Kanto WP (1988) Neonatal withdrawal symptoms after chronic maternal ingestion of caffeine. *Southern Medical Journal*, **81**, 1092-1094. In: James JE (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Miller RC et al (1994) Acute maternal and foetal cardiovascular effects of caffeine. *Am J Perinatol*; **11**:132-6.

Miners JO and Birkett DJ. (1996) The use of caffeine as a metabolic probe for human drug metabolizing enzymes. *Gen Pharmac* 1996; **27**: 245-249.

Miners JO and McKinnon RA. (2000) CYP1A. In: *Metabolic Drug Interactions*. eds Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum ME, New York: Lippincott Williams & Wilkins, 2000: chapter 6, pp 61-73.

Mitchell P. J. and Redman J. R. (1992) Effects of caffeine, time of day and user history on study-related performance. *Psychopharmacology* **109,** 121-126.

Myers, D.E., Shaikh, Z. and Zullo, T.G. (1997) Hypoalgesic effect of caffeine in experimental ischemic muscle contraction pain. *Headache.* **37**: 654-658.

Naismith DJ, Akinyanju PA, Szanto S and Yudkin J (1970) The effect in volunteers of coffee and decaffeinated coffee on blood glucose, insulin, plasma lipids, and some factors involved in blood clotting, *Nutrition and Metabolism*, **12**, 144-151.

Nehlig A (1999a) Caffeine does not activate the brain structures involved in drug addiction. An abstract from a paper presented at the ASIC, 2-6 August 1999, Helsinki.

Nehlig, A (1999b) Are we dependent upon coffee and caffeine? A review of human and

animal data. *Neuroscience and Biobehavioural Reviews*, **23**, 563-576.

Nehlig, A., Daval, J.L., Boyet, S. and Vert, P. (1986) Comparative effects of acute and chronic administration of caffeine on local cerebral glucose utilization in the conscious rat. *European Journal of Pharmacology.* **129**: 93-103.

Nehlig, A. and Debry, G. (1994) Effects of coffee on the central nervous system. In G. Debry (Ed), *Coffee and Health.* John Libbey, Montrouge, pp. 157-249.

Nehlig A and Debry G (1994 a) Potential teratogenic and neurodevelopmental consequences of coffee and caffeine exposure: a review of human and animal data. *Neurotoxicology and Teratology*, **16**, 531-543.

Nehlig A and Debry G (1994 b) Potential genotoxic, mutagenic and anti-mutagenic effects of coffee: a review. *Mutation Research*, **317**, 145-162.

Nehlig A, Daval J, Debry G (1992) Caffeine and the central nervous system: mechansisms of action, biochemical, metabolic and pyschostimulant effects. *Brain Res Rev*, **17**, 139-170.

Newton R, Broughton LJ, Lind MJ, Morrison PJ, Rogers HJ, Bradbrook ID. (1981) Plasma and salivary pharmacokinetics of caffeine in man. *Eur J Clin Pharmacol*; **21**: 45-52.

Ogilvie RI. (1978) Clinical pharmacokinetics of theophylline. *Clin Pharmacokinet*; **3**: 267-293.

Phillips-Bute BG & Lane JD. (1998) Caffeine withdrawal symptoms following brief caffeine deprivation. *Physiol Behav*; **63**:35-39

Phillis JW, Wu PH and Coffine VL. (1983) Inhibition of adenosine uptake into rat brain synaptosomes by prostaglandins, benzodiazepines and other centrally active compounds. *General Pharmacology*, **14**, 475-479. In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Pizziol A et al. (1998) Effects of caffeine on glucose tolerance: a placebo controlled study. *Europ J Clin Nurtr*; **52**:846-9.

Rachima-Maoz, C., Peleg, E. and Rosenthal, T. (1998) The effects of caffeine on ambulatory blood pressure in hypertensive patients. *American Journal of Hypertension.* **11**: 1426-1432.

Racotta, I.S., Leblanc, J. and Richard, D. (1994) The effect of caffeine on food intake in rats: Involvement of corticotropin-releasing factor and the sympatho-adrenal system. *Pharmacology, Biochemistry and Behavior*. **48**: 887-892.

Rachima-maoz C et al., (1998). The effect of caffeine on ambulatory blood pressure in hypertensive patients. *Am J Hyperten*. ; **11**:1426-32.

Rees, K., Allen, D. and Lader, M. (1999) The influences of age and caffeine on psychomotor performance. *Psychopharmacology.* **145**: 181-188.

Regina E. G., Smith G. M., Keiper C. G. and McKelvey R. K. (1974) Effects of caffeine on alertness in simulated automobile driving. *Journal of Applied Psychology* **59,** 483-489.

Revelle W., Anderson J. K. and Humphries M. S. (1987) Empirical tests and theoretical extensions of arousal-based theories of personality. In *Personality Dimensions and Arousal.* Edited by J. Strelau and H. J. Eysenck. Plenum Press, London.

Rihs, M., Muller, C. and Baumann, P. (1996) Caffeine consumption in hospitalized psychiatric patients. *European Archives of Psychiatry and Clinical Neurosciences.* **246**: 83-92.

Roache JD and Griffiths RR (1987) Interactions of diazepam and caffeine: behavioural and subjective dose effects in humans. *Pharmacology, Biochemistry and Behaviour*, **26**: In: James J. E. (1997b) Understanding Caffeine. A Biobehavioural analysis. Behavioural Medicine and Health Psychology Series. Sage publications.

Robelin, M. and Rogers, P.J. (1998) Mood and psychomotor performance effects of the first, but not of subsequent, cup-of-coffee equivalent doses of caffeine consumed after overnight caffeine abstinence. *Behavioural Pharmacology.* **9**: 611-618.

Rogers P. J., Richardson N. J. and Dernoncourt C. (1995) Caffeine use: Is there a net benefit for mood and psychomotor performance? *Neuropsychobiology* **31,** 195-199.

Rogers, P.J. and Dernoncourt, C. (1998) Regular caffeine consumption: A balance of adverse and beneficial effects for mood and psychomotor performance. *Pharmacology, Biochemistry and Behavior.* **59**: 1039-1045.

Rogers, P.J., Richardson, N.J. and Elliman, N.A. (1995) Overnight caffeine abstinence and negative reinforcement of preference for caffeine-containing drinks. *Psychopharmacology.* **120**: 457-462.

Rubin,G.J. and Smith,A.P. (1999) Caffeine withdrawal and headaches. *Nutritional Neuroscience* **2**, 123-126.

Ruijter, J., Lorist, M.M. and Snel, J. (1999) The influence of different doses of caffeine on visual task performance. *Journal of Psychophysiology.* **13**: 37-48.

Santos IS, Victoria CG, Huttly S and Carvalhal JB (1998) Caffeine intake and low birth weight: a population-based case-control study. *American Journal of Epidemiology*, **147**, 620-62.

Scott NR, Stambuck D, Chakraborty J et al (1988) Caffeine clearance and biotransformation in patients with chronic liver disease. *Clinical Science*, **74**: 377-384. In: James, J.E. (1991) *Caffeine and Health.* Academic Press, London. pp. 1-432.

Scott NR, Stambuck D, Chakraborty J et al (1989) The pharmacokinetics of caffeine and its dimethylxanthine metabolites in patients with chronic liver disease. *British Journal of*

Clinical Pharmacology, **27**: 2-5-213. In: James, J.E. (1991) *Caffeine and Health.* Academic Press, London. pp. 1-432.

Setchell KDR, Welsh MB, Klooster MJ, Balistreri WF, Lim CK (1987) Rapid high-performance liquid chromatography assay for salivary and serum caffeine following an oral load. An indicator of liver function. *J Chromatogr*; **385**: 267-274.

Shi, D., Nikodiijevic, O., Jacobson, K.A. and Daly, J..W. (1993) Chronic caffeine alters the density of adenosine, adrenergic, cholinergic, GABA and serotonin receptors and calcium channels in mouse brain. *Cellular and Molecular Neurobiology.* **13**: 247-261.

Silverman K., Evans S. M., Strain E. C. and Griffiths R. R. (1992) Withdrawal syndrome after the double-blind cessation of caffeine consumption. *New England Journal of Medicine* **327,** 1109-1114.

Silverman, K., Mumford, G.K. and Griffiths, R.R. (1994) Enhancing caffeine reinforcement by behavioral requirements following drug ingestion. *Psychopharmacology.* **114**: 424-432.

Smith A. (1994) Caffeine, performance, mood and states of reduced alertness. Special Issue: Caffeine research. *Pharmacopsychoecologia* **7,** 75-86.

Smith A. P. (1996a) Caffeine dependence: An alternative view. *Nature Medicine* **2,** 494.

Smith A. P., Kendrick A. M. and Maben A. L. (1992) Effects of breakfast and caffeine on performance and mood in the late morning and after lunch. *Neuropsychobiology* **26,** 198-204.

Smith A. P., Brockman B., Flynn R., Maben A. and Thomas M. (1993a) Investigation of the effects of coffee on alertness and performance during the day and night. *Neuropsychobiology* **27,** 217-223.

Smith A. P., Maben A. and Brockman P. (1993b) The effects of caffeine and evening meals on sleep and performance, mood and cardiovascular functioning the following day. *Journal of Psychopharmacology* **7,** 203-206.

Smith, A.P., Clark, R. and Gallagher, J. (1999) Breakfast cereal and caffeinated coffee: Effects on working memory, attention, mood and cardiovascular function. *Physiology and Behavior.* 67: 9-17.

Statland BE and Demas TJ. (1980) Serum caffeine half-lives. Healthy subjects vs patients having alcoholic hepatic disease. *American Journal of Clinical Pathology*, **73**: 390. In: James, J.E. (1991) *Caffeine and Health.* Academic Press, London. pp. 1-432.

Statland BE, Demas T and Danis M. (1976) Caffeine accumulation associated with alcoholic liver disease. *New England Journal of Medicine*, **295**: 110-111. In: James, J.E. (1991) *Caffeine and Health.* Academic Press, London. pp. 1-432.

Stavric B. (1992) An update on research with coffee/caffeine. *Food and Chemical Toxicology*, **30**, 533-555.

Strain, E.C., Mumford, G.K., Silverman, K. and Griffiths, R.R. (1994) Caffeine dependence syndrome: Evidence from case histories and experimental evaluations. *Journal of the American Medical Association.* 272: 1043-1048.

Svenningsson, P., Nergardh, R. and Fredholm, B.B. (1998) Regional differences in the ability of caffeine to affect haloperidol-induced striatal c-fos mRNA expression in the rat. *Neuropharmacology.* **37**: 331-337.

Tang BK and Kalow W. (1996) Assays for CYP1A2 by testing *in vivo* metabolism of caffeine in humans. *Methods Enzymol*; **272**: 124-131.

Tarrus E, Cami J, Spickett RG *et al* (1987) Accumulation of caffeine in healthy volunteers treated with furafylline. *British Journal of Pharmacology*, **23**, 9-18.

Tassaneeyakul W, Mohamed Z, Birkett DJ, McManus ME, Veronese ME, Rukey RH, Quattrochi LC, Gonzalez FJ, Miners JO. (1992) Caffeine as a probe for human cytochromes P450: validation using cDNA-expression, immunoinhibition and microsomal kinetic and inhibitor techniques. *Pharmacogenetics*; **2**: 173-183.

Tassaneeyakul W, Birkett DJ, McManus ME, Tassaneeyakul W, Veronese ME, Andersson T, Tukey RH, Miners JO. (1994) Caffeine metabolism by human hepatic cytochromes P450: contributions of 1A2, 2E1 and 3A isoforms. *Biochem Pharmacol* ; **47**: 1767-1776.

Thelle, D.S., Heyden, S. and Fodor, J.G. (1987) Coffee and cholesterol in epidemiological and experimental studies. *Atherosclerosis.* **67**: 97-103.

Thomas DB (1988) Neonatal abstinence syndrome [letter to the editor]. *Medical Journal of Australia*, **148**, 598.

Ullrich D, Compagnone D, Munch B, Brandes A, Hille H, Bircher J (1992) Urinary caffeine metabolites in man. *Eur J Clin Pharmacol*; **43**: 167-172.

Urgert, R. and Katan, M.B. (1997) The cholesterol-raising factor from coffee beans. *Annual Review of Nutrition.***17**: 305-324.

Wahllander A, Renner E, Karlaganis G and Preisig R (1983) CNS-effects of caffeine in cirrhotics measured by an extended flicker fusion (De Lange) test. *Experienti*a, **39**: 684. In: James, J.E. (1991) *Caffeine and Health.* Academic Press, London. pp. 1-432.

Warburton, D.M. (1995) Effects of caffeine on cognition and mood without caffeine abstinence. *Psychopharmacology.* **119**: 66-70.

Vlajinac HD, Petrovic RR and Marinkovic JM *et al* (1997) Effect of caffeine intake during pregnancy on birth weight. *American Journal of Epidemiology*, **145**, 335-338.

Wright KP Jr et al. (1997) Caffeine and light effects on night time melatonin and temperature levels in sleep-deprived humans. *Brain Res*; **747**: 78-84.

References for epidemiological studies of the effect of caffeine on hypertension and cardiovascular disease

Chou TM and Benowitz NL (1994) Caffeine and coffee-effects on health and cardiovascular disease. *Comparative Biochem Physiol-C:Comparative Pharmacol Toxicol*. ; **109**:173-89.

Jee SH et al (1999) The effect of chronic coffee drinking on blood pressure- a meta-analysis of controlled clinical trials. *Hypertension*; **33**:647-52.

Green PJ et al (1986) The effects of caffeine on blood pressure and heart rate- a review. *Ann Behav Med*; **18**:201-16.

Gyntelberg F et al (1995) Coffee consumption and risk of ischaemic heart disease- a settled issue. *J Intern Med*; **237**:55-61.

Hakim AA et al (1998) Coffee consumption in hypertensive men in older middle-age and the risk of stroke- The Honolulu Heart Program. *J Clin Epidemiol*; **51**:487-94.

Kawachi I et al (1994) Does coffee drinking increase the risk of coronary heart disease- results from a meta-analysis. *Br Heart J*; **72**:269-75.

Lamarine RJ (1994) Selected health and behavioural effects related to the use of caffeine. *J Comm Health*; **19**:449-66.

Lewis CE et al (1993) Inconsistent associations of caffeine-containing beverages with blood pressure and with lipoproteins- The Cartia Study. *Am J Epidemiol*; **138**:502-7.

Narkiewicz K et al (1995) Interactive effect of cigarettes and coffee on daytime systolic blood pressure in patients with mild essential hypertension. *J Hyperten*; 13:965-70.

Nurminen ML et al (1999) Coffee, caffeine and blood pressure: a critical review. *Europ J Clin Nutrition*; **53**:831-9.

Palatini P et al. (1996) Relationship of plasma renin activity with caffeine intake and physical training in mild hypertensive men. *Eur J Epidemiol*; **12**:485-91.

Palmer JR et al (1995) Coffee consumption and myocardial infarction in women. *Am J Epidemiol*; **141**:724-31.

Sesso HD et al (1999) Coffee and tea intake and the risk of myocardial infarction. *Am J Epidemiol*; **149**:162-7.

Stamler J et al (1996) Relationship to blood pressure of combinations of dietary macronutrients- findings of the multiple risk factor intervention trial (MRFIT). *Circulation*; **94**:2417-23.

Stamler J et al (1997) Relation of body mass and alcohol, nutrient, fiber, and caffeine intakes to blood pressure in the special intervention and usual care groups in the multiple risk factor intervention trial. *Am J Clin Nutr*; **65(Suppl 1**):338-65.

Wakabayashi K et al (1998) Habitual coffee consumption and blood pressure: A study of self-defence officials in Japan. *Europ J Epidemiol*: 14: 669-73.

Weinmann S et al (1997) Caffeine intake in relation to the risk of primary cardiac arrest. *Epidemiol*; 8:505-8.

APPENDIX 1

Literature Review

A review of studies of caffeine dose or concentrations and physiological or toxic effects were identified from a medline search. The search was limited to English articles published between 1991-1999 on human subjects. Publications identified included studies of acute and chronic caffeine ingestion as well as caffeine withdrawal. The articles are summarised in the following pages under the headings Metabolic effects, Sleep effects, Foetal Effects, Cardiovascular effects, Psychomotor effects, Tremor, Headaches, Anxiety and Physical dependency and withdrawal. Most of the articles were randomised control trials with small numbers of subjects. The studies examined the acute or chronic effects of oral or intravenous caffeine administered at doses that ranged from 37.5mg to 547mg in normal younger or elderly volunteers as well as patients with asthma, poor sleepers, pregnant women, patients with hypertension or heart disease, infants and children.

Several variables need to be considered when interpreting studies with caffeine these include the pharmacokinetics (eg age and sex differences, pregnancy, liver disease, diet, smoking and concomitant drug therapy), the source of caffeine (eg caffeinated beverages such as coffee may have physiological effects related to other constituents), the study design, the population studied and the sample size. Although larger controlled studies are required to confirm the dose related effects of caffeine there appears to be enhanced performance and mood effects from doses of 37.5mg, the appearance of cardiac effects in pregnant women at doses of 90mg and increased anxiety in children at doses of 95mg and 210mg in adults. Sleep effects are reported following 100mg at bedtime and effects on diastolic blood pressure and free fatty acids at doses of 140mg.

REFERENCE	STUDY DESIGN	POPULATION	OUTCOMES	CONCLUSION
Metabolic effects				
Pizziol A et al. ***Effects of caffeine on glucose tolerance: a placebo controlled study.*** *Europ J Clin Nurtr 1998; 52:846-9.*	Single blind Latin square study of **200mg caffeine** or placebo on glucose tolerance in non-smoking healthy subjects who abstained from caffeine for 4 weeks.	30 healthy subjects 26-32 years.	The glycaemic curve was shifted to the right at 2, 3, 5 hours post caffeine compared to placebo. Blood insulin levels were comparable after caffeine and placebo along entire oral glucose tolerance test.	200mg caffeine intake induces an insulin independent rise in blood glucose levels.
Wright KP Jr et al. ***Caffeine and light effects on nighttime melatonin and temperature levels in sleep-deprived humans****. Brain Res 1997; 747: 78-84.*	Randomised placebo controlled study of **200mg caffeine** twice each night and dim or bright light in subjects during 45.5h sleep deprivation period on melatonin levels and body (tympanic) temperature.	40 male subjects, mean 19.2 years (range 18-25 years) who typically consumed 50-200mg caffeine/day following 24 hours of abstinence	Dim light-caffeine suppressed night-time melatonin levels and attenuated the normal decrease in temperature compared to placebo. Bright light-caffeine suppressed melatonin and attenuated the normal night-time drop in temperature > caffeine or bright light alone > dim light-placebo.	Two 200mg doses caffeine affected melatonin system and temperature levels in sleep deprived subjects.
Lovallo WR et al. ***Stress-like adenocorticotropin responses to caffeine in young healthy men.*** *Pharmacol, Biochem Behav 1996; 55:365-9.*	Double-blind placebo controlled cross-over study of **3.3mg/kg caffeine** (equivalent to 2-3 cups coffee) on plasma adrenocorticotropin (ACTH) and cortisol (CORT) in health young men.	47 healthy young men.	Caffeine administration significantly elevated ACTH from 30 min to 180 min ($p<0.01$) and CORT from 60 min to 120 min ($p<0.01$). At 60 min ACTH increased 33% (+5.2pg/ml) and CORT 30% (+2.7 mcg/dl) compared to placebo	3.3mg/kg caffeine activates components of the pituitary-adrenocortical response: increasing ACTH release and CORT production.
Arciero PJ et al. ***Effects of caffeine ingestion on NE kinetics, fat oxidation, and energy expenditure in younger and older men.*** *Am J Physiol 1995; 268:1192-8.*	Double-blind placebo controlled study of 5mg/kg caffeine ingestion in older and younger moderate consumers (mean of 126mg/day and 160mg/day respectively) on energy expenditure, fatty acids and norepinephrine.	10 older subjects 65-80 years and 10 younger subjects 19-26 years. Plasma caffeine levels.	Plasma caffeine levels increased from 89±100 to 6340±1938ng/ml ($p<0.05$) in younger and 124±38 to 7066±2366ng/ml ($p<0.05$) in older men **There was an 11% increases in energy expenditure in younger men ($p<0.05$) from baseline and 9.5% in older men ($p<0.05$).** Caffeine increased fatty acid conc ($p<0.05$) and rate of appearance of fatty acids ($p=0.07$) in younger men but not older men. Rates of fat oxidation and NE appearance and clearance did not differ from baseline in either group.	Thermogenic responses to caffeine were similar however older men have a smaller increase in fatty acid availability after caffeine. Caffeine dose not given in abstract.
Kynast-Gales SA, Massey LK. ***Effect of caffeine on circadian excretion of urinary calcium****. J Am Coll Nut 1994; 15:467-72*	Open study on 2 consecutive days of morning **caffeine** (**3mg/kg** at 7am and 10am) or abstinence and later renal conservation on Ca and Mg excretion. Measurement of salivary caffeine, urinary Ca, Mg, Na and creatinine in subjects on a controlled diet.	17 healthy volunteers (males and females), 17-41 years.	Peak salivary caffeine 4.7umol/ml at 11.30am. Half-life 7.3h. No difference in creatinine excretion. Significant increase in urinary Ca and Mg ($p=0.01$, $p=0.04$) for 6 hours after the second caffeine dose. Caffeine induced mineral loss resulted in net 24-h urinary increases of 0.32mmol Ca and 0.16mmol Mg.	Night-time compensatory renal conservation was insufficient to offset morning caffeine-induced mineral losses following 2 morning doses of 3mg/kg caffeine.

Massey LK et al. ***Interactions between dietary caffeine and calcium on calcium and bone metabolism in women****. J Am Coll Nutr 1994; 13: 592-6.*	Study of effects of 2 weeks **caffeine abstinence** on calcium and bone metabolism in women habitually consuming 200mg/day caffeine and either low (414-584mg/day) or moderate Ca (662-1357mg/day).	25 women mean 65 years (range:39-76y)	There was no differences in dietary Ca intakes during caffeine and caffeine free periods in either group. Fasting total serum Ca, urinary hydroxyproline/creatinine and Ca/creatinine ration were unchanged in both groups. Women in low Ca group had significantly higher serum unfilterable Ca levels ($p<0.01$) and lower serum bone isoenzyme alkaline phosphatase levels after abstinence ($p<0.05$) whilst there was no difference in the moderate Ca group. Three-day mean urinary Ca excretion decreased after caffeine abstinence only in the moderate Ca group.	Abstinence from moderate caffeine intake raises ultrafiltrable Ca and decreases bone alkaline phosphatas in older women consuming <600mg Ca.
*Pianosi P et al****. Effect of caffeine on the ventilatory response to inhaled carbon dioxide.*** *Resp Physiol 1994; 95:311-20.*	Randomised double blind cross-over study of **5mg/kg caffeine** or saline on hypercapnic ventilatory response using steady state and rebreathing and serum caffeine levels.	6 subjects	There was significant ($p<0.05$) increase in the slope of the PETCO2 and VE measured by rebreathing (0.21 ± 0.14 to 0.38 ± 0.14 vital capacity/min.mmHg) and steady-state (0.23 ± 0.12 to 0.59 ± 0.45 vital capacity/min.mmHg). There was a parallel shift of VT vs PETCO2 measured by rebreathing and an increased slope in VT-PETCO2 measured by SS.	Caffeine acts as a respiratory stimulant and increases hypercapnic ventilatory response. The caffeine-CO2 interaction depends on the methodology used.
Henderson JC et al. ***Decrease of histamine induced bronchoconstriction by caffeine in mild asthma.*** *Thorax 1993; 48:824-6.*	Double blind placebo controlled study of single oral dose of **caffeine 5mg/kg** on FEV1 and bronchial responsiveness to histamine in mild stable asthma patients.	8 mild stable asthma patients.	Caffeine had no effect on FEV1. Mean log PC20 histamine was significantly higher at 150 minutes and 240 minutes after caffeine than placebo.	5mg/kg caffeine may interfere with bronchial provocation testing.

REFERENCE	STUDY DESIGN	POPULATION	OUTCOMES	CONCLUSION
Sleep effects				
Landolt HP et al. ***Caffeine intake (200mg) in the morning affects human sleep and EEG power spectra at night****. Brain Res 1995; 675:67-74.*	Placebo controlled study of **200mg caffeine** at 07.10h, salivary caffeine levels and sleep stages and EEG during subsequent night.	Nine healthy men.	Maximal caffeine saliva levels 17mumol/l 1 hour post dose to 3mumol/l immediately prior to sleep (23.00h). Sleep efficiency and total sleep time significantly lower with caffeine compared to placebo. EEG power density suppressed at 0.25-0.5Hz for nonREM and 0.75-4.5 and 5.25-6.0 Hz in REM sleep. In nonREM frequency range of sleep spindles (11.25-12.0 Hz and 13.25-14.0 Hz) was enhanced.	Saliva caffeine levels of 3mumol/l following a single dose of 200mg in the morning affect sleep.
Landolt HP et al. ***Caffeine reduces low-frequency delta activity in the human sleep EEG.*** *Neuropsychopharmacol 1995; 12:229-38.*	Placebo controlled study of **100mg caffeine** at bedtime on sleep and sleep EEG.	8 young males	Caffeine saliva levels decreased from 7.5mumol/l in 1st h sleep to 3.5 mumol/l in 7th hour.Caffeine prolonged sleep latency and reduced sleep efficiency and stage 4 of non-REM sleep.	100mg of caffeine at bedtime affects sleep EEG.
Tiffin P et al. ***Pharmacokinetic and pharmacodynamic responses to caffeine in poor and normal sleepers.*** *Psychopharmacol 1995; 121:494-502.*	Comparative study of pre and post **2.5mg/kg caffeine** in health poor sleepers and normal sleepers with similar daily caffeine consumption. Salivary caffeine levels, heart rate, blood pressure, visual analogue scales for concentration, vigilance and relaxation, psychomotor performance (Digital Symbol Substitution Test -DSST and tapping rate-TR) and EEG activity (Contingent negative variation- CNV, auditory evoked potential and power spectral analysis).	10 health self-rated poor sleepers and 10 normal sleepers.	Caffeine pharmacokinetics showed a significantly greater variability in Cmax, clearance and half-life in poor sleepers compared to normals. Poor sleepers had faster HR, lower concentration and relaxation ratings, poorer performance on DSST, greater CNV magnitude, faster peak alpha frequency and lower delta, theta and beta power both pre caffeine and after caffeine ingestion. Overall differences in these measures were significantly different compared to normals ($p<0.01$). For vigilance and TR only post dose scores in poor sleepers were significantly lower to normals.	Similar changes in pharmacodynamic measures in poor and normal sleepers following a 2.5mg/kg caffeine dose.

REFERENCE	STUDY DESIGN	POPULATION	OUTCOMES	CONCLUSION
Foetal Effects				
Cook DG et al. ***Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study***. Br Med J 1996; 313: 1358-62.	Prospective population based study of plasma caffeine concentrations in stored blood samples from pregnancy women attending inner London hospital between 1982-84, reported caffeine intake and birth weight adjusted for gestational age, maternal height, parity and sex of infant. Cigarette smoking was assessed using blood cotinine levels. Multiple regression analysis.	1,500 women who had provided a blood sample on at least 1 occasion and 640 women with blood samples at booking, 28 weeks and 36 weeks.	Caffeine intake did not change during pregnancy (2323±1458mg/week at booking, 2605±1375mg/week at 28 weeks, 2427±1480mg/week at 36 weeks) but blood caffeine levels increased 75% (2.3±1.68mcg/ml, 3.20±2.04mcg/ml, 4.12±2.76mcg/ml). Caffeine intake increased with blood cotinine concentrations >15ng/ml but blood caffeine levels decreased. Caffeine consumption was inversely related to adjusted birth weight- 1.3% fall birth weight for 1,000mg per week increased intake (95% CI 0.5%-2.1%). A caffeine effect was confined to smokers, -1.6%/1000mg a week (-2.9% to -0.2%) after adjustment for cotinine, -1.3% (-2.7% - 0.1%) after further adjustment for social class and alcohol. Adjusted birth weight was unrelated to blood caffeine levels during pregnancy (p=0.09), after adjustment for cotinine (p=0.73) or among current smokers (p=0.45).	Blood caffeine levels following ~300mg caffeine/day increased during pregnancy however they were not related to foetal growth. Caffeine intake showed a weak negative associated with birth weight in smokers.
Miller RC et al. ***Acute maternal and fetal cardiovascular effects of caffeine.*** Am J Perinatol 1994; 11:132-6.	Pre-post study of **caffeine 100mg/m^2** body surface area in caffeine naïve gravidas at 25.7 and 36.1 weeks on cardiovascular parameters.	7 pregnant women at 25.7 and 36.1 weeks (body surface area 1.78±0.14m^2, 1.86±0.16m^2)	Significant decreases in maternal pulse (85.1 vs 74.2beats/min, p=0.00003) and foetal HR (p=0.007), and increases in diastolic BP (p=0.005), mean arterial BP (p=0.008), uterine artery systolic-to-diastolic ratio (p=0.03), fetal heart rate accelerations (p=0.04) and fetal aortic peak velocities (p=0.002). Differences in systolic BP, fetal aortic and umbilical artery systolic-to-diastolic ratios were not significant.	Moderate caffeine intake (90mg) affects both fetal and maternal cardiovascular systems

REFERENCE	STUDY DESIGN	POPULATION	OUTCOMES	CONCLUSION
Cardiovascular effects				
Rachima-maoz C et al. ***The effect of caffeine on ambulatory blood pressure in hypertensive patients.*** Am J Hyperten 1998; 11:1426-32	Open study of **250mg caffeine** in hypertensive patients abstaining from caffeine for 2-3 weeks. Caffeine blood levels and blood pressure, blood renin, endothelin, urinary electrolytes and catecholamines.	23 hypertensive patients	Significant increase in systolic (p=0.017) and diastolic BP (p=0.023) occurred in 13 subjects mean age 58±10.4y. Non-responders were younger (44.5±15.8y). There was a significant decrease in HR during the first hour in responders (p=0.008) and non-responders (p=0.004). Marked diuresis and natriuresis occurred in both in first 6 hours. Renin and endothelin levels were unchanged.	250mg caffeine has acute effects on HR, diuresis and naturesis in hypertensive patients and BP effects in older patients.
Donnerstein RL et al. ***Acute effects of caffeine ingestion on signal-averaged electrograms.*** Am Heart J 1998; 136:643-6.	Randomised double blind crossover study of **5mg/kg caffeine** or placebo in normal subjects on signal-averaged electrocardiograms.	12 subjects (6 males, 6 female), 21-26 years.	Mean caffeine saliva levels 90 minutes post dose were 6.6±1.6mcg/dL. Signal-averaged P-wave and QRS complex durations did not significantly change after placebo. After caffeine ingestion QRS duration was prolonged in 9 of 11 subjects at 90 min ($p<0.02$) and in 8 of 9 after 3 h ($p<0.001$). P-wave duration and HR did not significantly change after caffeine.	5mg/kg caffeine ingestion produces a small but statistically significant prolongation of signal-averaged QRS complexes.
Arciero PJ et al. ***Relationship of blood pressure, heart rate and behavioural mood state to norepinephrine kinetics in younger and older men following caffeine ingestion.*** Europ J Clin Nutr 1998; 52:805-12.	Double-blind placebo controlled study of age-related differences in BP, HR, behavioural mood state and norepinephrine kinetics after **caffeine 5mg/kg**. Plasma glucose, insulin, caffeine levels.	10 males (65-80 years) and 10 males (19-26 years) who were moderate consumers of caffeine.	Plasma caffeine levels following caffeine ingestion were similar in older and younger males. Systolic BP increased by 9% ($p<0.01$) and diastolic BP 3% ($p<0.01$) in older men following caffeine but was unchanged in younger men. HR was unaltered in both groups after caffeine. Self-reported feelings of tension ($p<0.05$) and anger ($p=0.06$) decreased in older men while anger increased in younger men ($p<0.06$). No diff at baseline for norepinephrine conc, appearance and clearance between both groups. After caffeine norepinephrine conc were greater in older men, appearance and clearance was unchanged.	Caffeine 5mg/kg effects on BP and mood not related to changes in norepinephrine kinetics. Effects of caffeine on BP are augmented in elderly
Lane JD et al. ***Caffeine raises blood pressure at work.*** Psychosomatic Med 1998; 60:327-30.	Double-blind randomised 2 day crossover study of **100mg and 500mg caffeine** on 6-9 hours ambulatory BP and HR during working activities in healthy non smoking habitual coffee drinkers.	21 subjects	Average workday BP (4mm Hg for systolic and 3mm Hg for diastolic) and HR (3 bpm) were significantly higher with the 500mg dose. The pressor effects were independent of changes in posture, physical activity or stress.	500mg caffeine had a greater effect on BP and HR than 100mg in chronic caffeine users

Phillips-Bute BG & Lane JD. ***Caffeine withdrawal symptoms following brief caffeine deprivation.*** Physiol Behav 1997; 63:35-39	Double-blind placebo controlled cross-over study of **250mg caffeine** or placebo after overnight abstinence on mood, withdrawal symptoms, psychomotor performance (computerised battery score) and blood pressure in habitual coffee drinkers	31 health non-smoking adult volunteers (18 female, 13 male), 26-52 years tested twice 4 hours after administration of placebo or caffeine	BP was 5-6mm Hg lower with caffeine deprivation ($p<0,001$ systolic, $p<0.004$ diastolic). Fatigue/inertia scores were higher on caffeine deprivation ($p<0.04$) and vigor/activity scores were lower ($p<0.01$). Headache was not affected by caffeine deprivation ($p>0.39$) There were no changes in psychomotor performance apart from a weak trend for lower scores on logical reasoning test ($p<0.15$).	Short periods of caffeine deprivation associated with decreased vigor, increased fatigue, increased sleepiness and yawning, lower BP.
Bender AM et al. ***Hemodynamic effects of acute caffeine ingestion in young adults.*** Am J Cardiol 1997; 79:696-9.	Double-blind placebo-controlled random cross-over study of **5mg/kg caffeine** (equivalent to 3-4 cups coffee) or placebo and salivary caffeine, ECG and Doppler echocardiograms. Measurements included aortic annulus dimension, left ventricular ejection time (LVET), left ventricular posterior wall thickness during both systole (LVPWs) and diastole (LVPWd), left ventricular internal dimension during systole (LVIDs) and diastole (LVIDd), ascending aortic velocity, cardiac output, end-sytolic pressure, shortening fraction (SF), pulse pressure, mean BP, systemic vascular resistance (SVR), velocity of circumferential fiber shortening (Vcf).	6 male and 6 female volunteers without heart disease, mean age 23.6$\pm$1.4years (range:21-28y).	Mean caffeine levels reached were 6.6$\pm$1.6 mcg/ml. Following caffeine 11 subjects reported increased alertness, 8 mild tremors and 4 nausea. Following placebo 2 reported increased alertness and 1 mild tremor. At 90min post caffeine the was a significant increase for Vcf (16.6%, $p<0.02$), Vcf corrected for heart rate (14.5%, $p<0.03$), SF (12.1%, $p<0.02$), LVPWT (8.1%, $p<0.04$). The Vcf corrected for heart rate did not return to baseline within 4.5h following caffeine.	There were significant increases in cardiac contractibility following acute caffeine 5mg/kg consumption which did not return to normal for at least 4.5h
Delrio G et al. ***Increased cardiovascular response to caffeine in perimenopausal women before and during estrogen therapy***. Eur J Endocrinol 1996; 135:598-603.	Study design not stated in abstract. Comparative study of cardiovascular and catecholamine response to 250mg caffeine in premenopausal women and perimenopausal without oestrogen replacement and after 4 months of oestrogen replacement.	9 perimenopausal and 9 premenopausal women. Systolic BP, diastolic BP, HR, plasma norepinephrine, epinephrine, glucose, insulin and free fatty acids were determined at 0, 15, 30, 45, 60, 90 and 120 min post dose.	No differences in basal values systolic or diastolic BP, HR, norepinephrine, epinephrine, insulin, glucose, FFA between perimenopausal before and after therapy and premenopausal. Caffeine induced higher increases in systolic (p,0.05) and diastolic BP ($p<0.05$) in perimenopausal women before and during oestrogen therapy compared to premenopausal. HR increased only in perimenopausal women before therapy ($p<0.03$)	Enhanced cardiovascular reactivity to 250mg caffeine in perimenopausal women.
Newby DE et al. ***Caffeine restriction has no role in the management of patients with symptomatic idiopathic ventricular premature beats.*** Heart 1996; 76:355-7.	Double-blind randomised 6 week study of caffeinated coffee and decaffeinated coffee during normal diet and caffeine intake and dietary caffeine restriction, serum caffeine concentrations and 24h ventricular premature beat frequency.	13 patients (12 females, 1 male), 47.8$\pm$4.5 years with symptomatic idiopathic premature beats	There were significant alterations in serum caffeine concentrations ($p<0.001$) which correlated with caffeine consumption ($r=0.07$, $p<0.001$). There was a small significant correlation between visual analogue palpitation scores and ventricular premature beat frequencies ($r=0.34$, $p=0.003$). There was no significant changes in palpitation scores or ventricular premature beat frequencies during the intervention weeks and no significant correlations between these variables and serum caffeine concentrations.	Caffeine restriction did not have a significant effect on ventricular premature beats.

Pincomb GA et al. ***Acute blood pressure elevations with caffeine in men with borderline systemic hypertension.*** Am J Cardiol 1996; 77:270-74.	Double-blind placebo controlled cross-over study of **caffeine 3mg/kg** (with grapefruit juice) in men who were borderline hypertensives or low-risk controls after a 12 hour abstinence from caffeine (50-800mg/day) replicated in 2 protocols with counterbalance for drug assignment. Plasma caffeine levels taken pre and post dose.	48 healthy men (age 20-35 years), 24 borderline hypertensives (systolic BP 140-160mm Hg and/or diastolic BP 90-99mm Hg) and 24 low risk controls with no parenteral history of hypertension and screening BP<130/85mm Hg	Post dose placebo caffeine levels ranged from 0-1.7mcg/ml, Caffeine predose levels were 0-2.0mcg/ml (mean 0.3+0.1mcg/ml), average post dose caffeine levels were 6.3+0.2mcg/ml in protocol 1 and 6.6+0.3mcg/ml in protocol 2. Post dose levels did not differ between groups and were not predictive of the magnitude of the cardiovascular response to caffeine. Caffeine-induced changes in diastolic BP were 2-3 times larger in borderline subjects than controls (+8.4 vs +3.8 mm Hg, $p<0.0001$) with larger changes in impedance-derived measures of systemic vascular resistance (+135 vs +45 $dynes_{s\ cm\ sup}^{-5}$, $p<0.004$). This effect was not seen for systolic BP and HR. Diastolic BP changes exceeded the median control response in 96% of borderline subjects. 33% borderline subjects achieved hypertensive BP after caffeine ingestion. With multiple regression analysis the best predictor of diastolic responsivity was hypertension group status ($r=0.73$, $p<0.0001$)	3.3mg/kg caffeine ingestion in borderline hypertensives is associated with an enhanced pressor effect.
Lovallo WR, Alabsi M. ***Caffeine and behavioural stress effects on blood pressure in borderline hypertensive caucasian men.*** Health Psychol 1996; 15:11-17.	Double-blind cross-over study of **3.3mg/kg caffeine** and a psychomotor stressor in men with borderline hypertension and controls.	24 men with borderline BP (≤140/90mm Hg, ≤160/95 mm Hg) and 24 controls (≤135/85mm Hg).	Men with borderline BP had larger BP increases to the task and greater combined effect with caffeine plus task (+15/+11mm Hg) than controls (+10/+6mm Hg). Stats not provided in abstract.	Caffeine 3.3mg/kg has a greater effect in borderline hypertensives and this effect is increased with behavioural stress.
Benowitz NL et al. ***Sympathomimetic effects of paraxanthine and caffeine in humans***. Clin Pharmacol Ther 1995; 58:684-91.	Double-blind cross-over study of caffeine (**2 or 4mg/kg**), placebo, paraxanthene (major caffeine metabolite at 2 or 4mg/kg) and diastolic BP, plasma epinephrine and free fatty acids after 3 days of methylxanthine abstinence.	12 volunteers	Caffeine and paraxanthine significantly increased diastolic BP, plasma epinephrine levels and free fatty acids. Caffeine and paraxanthine effects were similar at 4mg/kg but caffeine produced greater response at 2mg/kg.	Caffeine and its metabolite paraxanthine have similar pharmacologic activity. Dose effect from 2mg/kg to 4mg especially for paraxanthine.

Debrah K et al. ***Effect of acute and chronic caffeine use on the cerebrovascular, cardiovascular and hormonal responses to orthostasis in healthy volunteers.*** Clin Sci 1995; 89:475-80.	Double bind placebo controlled study of acute effects of 250mg caffeine and chronic effects of 6 days caffeine use on supine and tilt induced changes in middle cerebral artery velocity (Vmca), heart rate, blood pressure and counter-regulatory hormone levels (catecholamines, growth hormone, cortisol) in healthy volunteers.	9 healthy volunteers	In the supine position acute caffeine ingestion associated with a fall in Vmca compared to placebo (-11cm/s difference, 95%CI –17 to –6cm/s, $p<0.001$), a rise in mean arterial pressure (4mm Hg, 95%CI 1 –6mm Hg, $p<0.01$) and plasma adrenaline levels (138pmol/l, 95%CI 53-223pmol/l, $p<0.01$). After chronic caffeine use the pressor and adrenaline responses were significantly attenuated but not the drop in Vmca. On tilting to 70 degrees the fall in Vmca was significantly greater with placebo that acute caffeine ingestion ($p<0.01$), increments in HR, mean arterial pressure and hormone levels were unchanged by caffeine, adrenaline and noradrenaline responses to tilting were significantly augmented by acute caffeine ingestion ($p<0.01$, $p<0.05$). Chronic caffeine dosing did not alter the fall in Vmca associated with tilting but significantly attenuated the adrenaline response ($p<0.01$ compared with the acute study). Acute caffeine dosing and orthostasis are both associated with a reduction in Vmca and a rise in mean arterial pressure and adrenaline levels.	The acute effects of caffeine 250mg on mean arterial pressure and adrenaline but not on Vmca are lost with chronic dosing.
Fotherby MD et al. ***Sustained caffeine use has no pressor effect in the elderly.*** Cardiol Elderly 1994; 2:499-503.	Double-blind randomised placebo controlled study of hemodynamic and neurohumoral responses (14h ambulatory BP, plasma caffeine, noradrenaline, adrenaline, renin activity) to prolonged (4 weeks) 250mg caffeine twice daily in elderly patients on a caffeine free diet.	18 fit ambulatory elderly subjects (mean 78 years, range 68-86 years), 11 men and 7 women. Systolic BP 105 – 225mm Hg, diastolic 54 – 108mm Hg.	There was no significant changes in clinic or 24h ambulatory systolic or diastolic BP, HR, or in any of the pressor mechanisms between placebo and caffeine phases of the study. There was no correlation between baseline BP and change in BP between placebo and caffeine phases.	Chronic dosing with 500mg caffeine/day had no significant effect on clinic or 24h ambulatory BP in elderly subjects.
James JE. ***Chronic effects of habitual caffeine consumption on laboratory and ambulatory blood pressure levels***. J Cardiovasc Risk 1994; 1:159-64.	Double bind placebo controlled cross-over study of caffeine or placebo three times a day for 6 days and caffeine or placebo on the 7th day on blood pressure and heart rate. **Dose caffeine not stated in abstract only states moderate caffeine ingestion.**	36 healthy normotensive volunteers (men and women)	BP elevated after caffeine ingestion. BP was unchanged or decreased after period of abstinence from caffeine. There was a small decrease in peak pressor effects were decreased when caffeine ingested after habitual use (6.0/5.2 mmHg) compared to when they had been abstinent before ingestion (7.7/6.8 mmHg). Pressor effects persisted on caffeine-challenge days even when subjects had been consuming caffeine.	Habitual consumption diminishes but does not eliminate the pressor effects of caffeine . **Dose and statistics?**
Sung BH et al. ***Prolonged increases in blood pressure by a single oral dose of caffeine in mildly hypertensive men.*** Am J Hyperten 1994; 7:755-8.	Open comparative study of **3.3mg/kg caffeine** (equivalent to 2-3 cups coffee) on BP in hypertensive and normotensive men for 3h.	18 hypertensive men and 12 age matched normotensive men.	Systolic BP were significantly higher after caffeine for both groups for entire 3h ($p<0.001$). The hypertensive group had persistent elevation in diastolic BP for 3h. The increment of diastolic BP became smaller in the normotensive group after 90min.	3.3mg/kg caffeine significantly increases systolic BP.

Haigh RA et al. ***Duration of caffeine abstention influences the acute blood pressure responses to caffeine in elderly normotensives.*** Europ J Clin Pharmacol 1993; 44:549-53.	Placebo controlled study of acute **250mg** caffeine load on blood pressure over 120minutes after a 48 hour and 12 hour abstinence in elderly subjects	8 elderly normotensive regular caffeine users	**Plasma caffeine levels after an acute dose following a 48h and 12h abstinence were similar. Following 48h abstinence caffeine resulted in higher supine systolic BP (12.1mmHg, 95%CI 4.3-19.9mm Hg, p=0.008) and diastolic BP (7.4mm Hg, CI 3.6-11.2mmHg, p<0.001). Similar changes were seen in standing BP. The BP effects were greater after 48h abstinence than 12h.** Pulse rate was unchanged.	Caffeine has an acute pressor effect after a 48 but not 12 hour abstinence in elderly normotensives
Romagnoli C et al. ***Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants.*** Therapeutic Drug Monit 1992; 14:14-9.	Comparative study of **10mg/kg loading** dose followed by **5mg/kg or 2.5mg/kg caffeine citrate** in preventing apneic spells in premature infants	37 pre-term infants born before 32nd week of gestation	Significantly lower theophylline levels in 2.5mg/kg caffeine group. Significant decrease in number apneic spells in both treatment groups compared with controls. Caffeine 2.5mg/kg group significantly less side effects (tachycardia, GI intolerance) than 5mg/kg group.	Caffeine citrate 2.5mg/kg significantly decreases apneic spells with less side-effects.
Lovallo WR et al. ***Hypertension risk and caffeine's effect on cardiovascular activity during mental stress in young men.*** Health Psychol 1991: 10:236-43.	Placebo controlled study of **3.3mg/kg** caffeine in men at low risk and high risk for essential hypertension	19 low risk men (negative for parenteral hypertension and low-normal resting BP) and 20 high risk men (positive history and high normal BP)	Caffeine increased vascular resistance in both groups. During a 15min demanding psychomotor task there were increases in systolic BP, cardiac output with equivalent BP rises in both groups. Due to the higher resting BP in the high risk group 50% had a transient BP ≥140/90mm Hg.	3.3mg/kg caffeine with metal stress may produce undesirable BP in those at risk for hypertension.
MacDonald TM et al. ***Caffeine restriction: effect on mild hypertension.*** Br Med J 1991; 303:1235-8.	Randomised crossover trial of 2 week regimens of normal diet, caffeine free diet, caffeine free with decaffeinated coffee, caffeine free with caffeinated coffee in patients with untreated borderline or mild hypertension who normally drank ≤3 cups coffee/day. Measures mean ambulatory BP, mean morning, day-time and night-time ambulatory BP, sitting BP and plasma caffeine at 1700h.	52 patients (23 males, 29 females), 26-67 years.	Dietary compliance measured by caffeine levels was excellent. No difference in mean 24h ambulatory BP, BP variability between regimens. Morning ambulatory diastolic BP was 2.8mm Hg higher during caffeine free diet than caffeine free diet with caffeinated coffee. Mean sitting clinic BP was 4.7mm Hg higher with caffeine free diet than caffeine free with caffeinated coffee (p<0.05) No significant correlation between plasma caffeine concentrations and BP.	Two weeks of caffeinated coffee does not adversely influence BP in borderline or mild hypertension, abstinence was of no benefit
Myers MG , Reeves RA. ***The effect of caffeine on daytime ambulatory blood pressure.*** Am J Hyperten 1991; 4:427-31.	Open study of **400mg caffeine** daily on ambulatory blood pressure during normal activities.	25 normotensive caffeine naïve subjects	There was a small significant increase in ambulatory daytime BP (+3/+3 mm Hg, p<0.001) associated with a fall in HR (-3beats/min, p<0.02) on the first day with BP levels returning to baseline by day 3.	400mg caffeine daily caused a small increase in ambulatory blood pressure but tolerance developed by day 3

REFERENCE	STUDY DESIGN	POPULATION	OUTCOMES	CONCLUSION
Psychomotor Performance				
Bryant CA et al. ***Psychomotor performance: investigating the dose-response relationship for caffeine and theophylline in elderly volunteers***. Eur J Clin Pharmacol 1998; 54:309-13.	Double-bind randomised placebo controlled six period crossover study in elderly volunteers of 3 doses theophylline (predicted peak 3mg/l, 6mg/l and 12mg/l), 2 doses **caffeine (predicted peaks 4.5mg/l, 9mg/l)** and placebo and psychomotor performance (continuous attention task, symbol digit substitution test, choice reaction time)	10 healthy elderly volunteers.	Significant improvement on continuous attention task at lowest concentration of caffeine and theophylline. The effect was not increased at higher concentrations where there was a non-significant trend to placebo scores. There was little effect of either drug on the subjective effects measured by visual analogue scales	At low plasma concentrations caffeine (4.5mg/l) increased psychomotor performance measures of attention in healthy elderly.
Phillips-Bute BG & Lane JD. ***Caffeine withdrawal symptoms following brief caffeine deprivation***. Physiol Behav 1997; 63:35-39	Double-blind placebo controlled cross-over study of **250mg caffeine** or placebo after overnight abstinence on mood, withdrawal symptoms, psychomotor performance and blood pressure in habitual coffee drinkers	31 health non-smoking adult volunteers (18 female, 13 male), 26-52 years tested twice 4 hours after administration of placebo or caffeine	BP was 5-6mm Hg lower with caffeine deprivation ($p<0,001$ systolic, $p<0.004$ diastolic). Fatigue/inertia scores were higher on caffeine deprivation ($p<0.04$) and vigor/activity scores were lower ($p<0.01$). Headache was not affected by caffeine deprivation ($p>0.39$) There were no changes in psychomotor performance apart from a weak trend for lower scores on logical reasoning test ($p<0.15$).	Short periods of caffeine deprivation associated with decreased vigor, increased fatigue, increased sleepiness and yawning, lower BP.
Lane JD. ***Effects of brief caffeinated-beverage deprivation on mood, symptoms, and psychomotor performance.*** Pharmacol Biochem Behav 1997; 58:203-8.	Open cross-over study of ad lib caffeinated beverages or caffeine abstinence at midday on 2 consecutive days, mood, withdrawal symptoms and psychomotor performance. Mean estimated **caffeine intake 547mg/day**	10 male and 14 female volunteers, 32±8 years (range 22-49y).	Caffeine beverage deprivation associated with significant decreased vigor ($p<0.05$) and mean arterial BP ($p<0.05$) and increased fatigue ($p<0.05$) and symptoms including headache ($p<0.05$). No observed changes in psychomotor performance.	Even short periods caffeine deprivation can produce unpleasant effects by the middle of the day.
Kaplan GB et al. ***Dose-dependent pharmaco-kinetics and psychomotor effects of caffeine in humans.*** J Clin Pharmacol 1997; 37:693-703.	Double-blind randomised single-dose crossover study of **250mg and 500mg caffeine** and placebo on psychomotor effects.	12 healthy volunteers	Caffeine kinetics nonlinear with reduced clearance and longer half-life for 500mg dose. The 250mg dose produced more favourable subjective effects (elation, peacefulness, pleasantness) and the 500mg dose more unpleasant effects (tension, nervousness, anxiety, excitement, irritability, nausea, palpitations, restlessness). Performance enhancement: 250mg> placebo and 500mg. There was a concentration dependent increase in anxiety and improvements in cognitive and motor performance at low to intermediate concentrations. Changes in electrencephalographic amplitude were not dose-dependent.	Favourable subjective and performance-enhancing effects occurred at 250mg caffeine dose. Unfavourable subjective and somatic effects, performance disruption occur at 500mg caffeine dose.

Azcona O et al. ***Evaluation of the central effects of alcohol and caffeine interaction.*** Br J Clin Pharmacol 1995; 40:393-400.	Double-blind placebo controlled cross-over study of placebo, alcohol 0.8g/kg, **caffeine 400mg** and alcohol + caffeine, plasma levels and psychomotor performance, phamacodynamic tests. Psychomotor tests- critical flicker fusion, simple reaction time, tapping test. EEG, BP, HR and effects experienced as symptoms.	8 healthy male subjects age 23-27 years.	The AUC for caffeine was significantly greater when combined with alcohol than when taken alone ($p=0.027$). Cmax caffeine was 9.10±2.01mcg/ml and tmax was 95±29min Decrease in simple reaction time (SRT) with caffeine ($p=0.005$) and an increase in amplitude of the evoked potentials ($p=0.019$).	400mg caffeine produced a stimulant effect on CNS function significant in SRT and in the amplitudes of late visual evoked potential.
Richardson NJ et al. ***Mood and performance effects of caffeine in relation to acute and chronic caffeine deprivation.*** Pharmacol Biochem Behav 1995; 52:313-20.	Double-blind randomised study of **250mg, 70mg caffeine** and placebo following 90 minute, 13-15h and 7 day caffeine deprivation in subjects regularly consuming 200mg-1000mg/day and in non-consumers on mood (headache, tiredness, jittery ratings) and cognitive performance (hand steadiness, simple reaction time and intertap interval)..	67 volunteers (49 caffeine consumers and 18 non-consumers), 18-23years. Saliva samples were taken predose	Vaseline mood ratings for the 3 caffeine consumer groups were not significantly different ($p>0.05$). At headache ratings were significantly higher for the 7 day deprivation group ($p<0.05$) and cheerful ratings were lower ($p<0.05$). Acute caffeine intake affected withdrawn, non-withdrawn and non-consumers similarly. Rated headache and tiredness were higher after placebo ($p=0.07$, $p=0.07$), jittery ratings were higher after both doses of caffeine ($p=0.06$). Hand steadiness was decreased by caffeine in a dose-related manner ($p=0.01$) and simple reaction time task was enhanced by 70mg caffeine	70mg caffeine reduced tiredness and improved performance, 250mg reduced hand steadiness, increased jitteriness and reduced headache
Rush CR et al. ***Intravenous caffeine in stimulant drug abusers: subjective reports and physiological effects.*** J Pharmacol Exp Ther 1995; 273:351-8	Double blind study of **0, 37.5, 75, 150 and 300mg/70kg intravenous caffeine** twice according to a latin-square design in subjects with a history of stimulant drug abuse. Effects were measured pre-injection to 60 minutes post.	10 subjects	Dose-dependent increase in ratings of positive mood peaking at 2 minutes and then progressively decreasing Dose-dependent increase in frequency of stimulant identifications. Negative-mood effects were of smaller magnitude and significant only at highest dose. Increased reports of unusual smells and tastes Decrease in HR (7bpm), skin temperature (4C) and increase systolic BP (8mm Hg) and diastolic BP (6mm Hg)	No stats provided in abstract
Bovim G et al. ***Caffeine influence on the motor steadiness battery in neuropsychological tests.*** J Clin Exp Neuropsychol 1995; 17:472-6.	Randomised double blind crossover study of **300mg caffeine** on motor performance tests in females.	24 healthy females (23-38 years)	Significantly poorer motor steadiness performance after caffeine than placebo. Increased error time and error count after caffeine consumption. Caffeine tended to reduce maze coordination test performance.	300mg caffeine significantly reduced motor steadiness performance in healthy females.

Hansenfratz M, Battig K. ***Acute dose-effect relationships of caffeine and mental performance, EEG, cardiovascular and subjective parameters.*** Psychopharmacol 1994; 114:281-7.	Cross-over study of **0, 1.5, 3 and 6mg/kg caffeine** on mental performance (rapid information processing task- RIP), cardiovascular effects, EEG and mood parameters	20 female non-smoking regular coffee drinkers.	Dose-effect observed for alpha and beta-EEG frequencies, anxiety, wakefullness and some coffee ratings. Negative dose-effect relationship for RIP processing rate and BP. No dose-effect relationship for reaction time and motor activity.	No consistent dose-response relationship for all parameters. Different parameters respond at different range.
Bernstein GA et al. ***Caffeine effects on learning, performance and anxiety in normal school-age children.*** J Am Acad Child Adolesc Psych 1994; 33:407-15.	Double-blind randomised placebo controlled cross-over study of acute caffeine **2.5mg/kg and 5.0mg/kg** compared to baseline and placebo on learning, performance and anxiety in prepubertal children. Saliva samples were analysed for levels. Children were asked to abstain from caffeine drinks for 12-15 hours before each experimental session	21 children (12 boys, 9 girls), mean age 10.6 years (range 8-12 years) mean weight 38.1kg	Baseline caffeine on unrestricted diet was 425.1±715.3ng/ml. Caffeine levels after 2.5mg/kg were 2491.9±479ng/ml and after 5mg/kg were 4580.5±846.6ng/ml. **Caffeine significantly improved performance on 2 of 4 measures of the Test of Variables of Attention (omission errors p=0.005, variability of response p<0.001) and on a test of manual dexterity in the dominant hand.** Trend for increased self-reported visual analogue measure of anxiety (p=0.098). Children reported feeling less sluggish after caffeine than placebo (p=0.043).	Caffeine 2.5mg/kg and 5.0mg/kg enhanced performance on a test of attention and on a motor task, children were less sluggish but more anxious.
Dimpfel W et al. ***The influence of caffeine on human EEG under resting conditions and during mental loads.*** Clin Invest 1993;71:197-207	Placebo controlled pilot study of single oral doses of **200mg and 400mg caffeine** on CNS using quantitative EEG analysis.	10 healthy males, average age 21y.	Single oral 200mg and 400mg caffeine doses reduced EEG spectral power density especially of the theta and alpha ranges.	200mg and 400mg caffeine influenced the EEG in the theta and alpha ranges. Although effects of 200mg and 400mg differed there was no clear dose effect.
Silverman K, Griffiths RR. ***Low-dose caffeine discrimination and self-reported mood effects in normal volunteers.*** J Exp Anal Behav 1992; 57:91-107.	Double-blind study of **178mg caffeine** or placebo on discrimination and self-reported mood effects in caffeine-abstinent normal volunteers.	15 subjects tested at 15 minute intervals after caffeine ingestion	5 subjects acquired the caffeine versus placebo discrimination within the first 20 sessions and 6 required further training. Nine subjects were subsequently trained at lower doses. The lowest dose to produce discrimination also produced self-reported mood effects. 4 subjects showed discrimination and mood effects at 100mg, 2 at 56mg, 1 at 32mg, 1 at 18mg, 1 at 10mg.	Discriminatory and self-reported mood effects can occur at levels of 10mg caffeine.

Yu G et al. ***A comparison of the central nervous system effects of caffeine and theophylline in elderly subjects.*** Br J Clin Pharmacol 1991; 32:341-5.	Double-blind cross-over study of **250mg caffeine** or theophylline or placebo on subjective ratings and psychological test performance in healthy elderly subjects.	20 healthy elderly subjects	Plasma caffeine concentrations 5.76mg/L 2h post-dose. Significant improvement on continuous attention task with caffeine and theophylline compared to placebo. Performance with caffeine significantly better than theophylline. Mean error index scores lower with caffeine than theophylline and placebo. Subjects felt significantly more alert on caffeine than theophylline than placebo. Subjects rated themselves as more energetic on caffeine than placebo.	Caffeine improves performance in elderly subjects and is a CNS stimulant.

REFERENCE	STUDY DESIGN	POPULATION	OUTCOMES	CONCLUSION
Tremor				
Miller LS et al. ***Caffeine but not time of day, increases whole arm physiological tremor in non-smoking moderate users***. Clin Exp Pharmacol Physiol 1998; 25:131-3.	Randomised placebo controlled study of **1mg/kg or 3mg/kg caffeine** and time of day (08.00, 11.00, 14.00, 17.00, 20,00 or 23.00) on whole arm physiological tremor as a sensitive measure of physiological change	188 young adult males, non-smokers	Significant increase in whole-arm tremor at 3mg/kg but not 1mg/kg. Time of day or the interaction of caffeine and time of day did not affect physiological tremor.	Dose-effect demonstrated with caffeine on whole arm tremor between 1mg/kg and 3mg/kg
Headaches				
Couturier EG et al. ***Influence of caffeine and caffeine withdrawal on headache and cerebral blood flow velocities.*** Cephalagia 1997; 17:188-90.	Comparative study of headache, changes in blood flow velocity (BFV) measured by Transcranial Doppler sonography (TCD), and serum caffeine concentrations during regular caffeine intake, caffeine withdrawal and "re-caffeination"	20 healthy volunteers without a headache history.	10 subjects suffered moderate to severe headaches after 24h of caffeine abstinence that completely recovered within 1h of caffeine intake. BFV were statistically significantly higher in left cerebral basilar and both posterior cerebral arteries following the withdrawal period. BFV decreased significantly 1 hour after caffeine intake in all subjects and returned to baseline after 2h.	Demonstrates a relationship between caffeine withdrawal, development of headache and alterations in cerebral blood flow velocities.
Hampl KF et al. ***Perioperative administration of caffeine tablets for prevention of postopertive headaches.*** Can J Anaesth 1995; 42:789-92	Randomised control trial of caffeine tablets at a dose equal to individual daily intake or placebo in patients undergoing minor surgical procedures.	40 patients asked to refrain from all caffeine sources preoperatively (verified by blood sample)	10 patients who received placebo had headaches which persisted in 7 patients until the next day. No patient receiving caffeine tablets as substitution therapy reported headache following surgery and 1 reported headache on postop day 1	Prophylactic caffeine reduces headaches in patients accustomed to high daily caffeine intake
Anxiety				
NickeLL PV, Uhde TW. ***Dose-response effects of intravenous caffeine in normal volunteers.*** Anxiety 1994-95; 1:161-8.	Blinded dose-response study of **intravenous caffeine (3, 5 and 7mg/kg)** and placebo in normal control subjects on anxiety, blood levels cortisol and lactate	10 subjects	Olfactory hallucinations were experienced in all subjects immediately following IV caffeine infusion. Dose-related increases in ratings of anxiety and blood levels of cortisol and lactate.	Dose related caffeine effect on anxiety.

Physical dependency and Withdrawal				
Silverman K et al. ***Withdrawal syndrome after the double-blind cessation of caffeine consumption.*** N Engl J Med 1992; 327:1109-14.	Double-blind placebo controlled study of caffeine equivalent to daily consumption in adults consuming low to moderate caffeine (**mean 235mg/day**) following a two day abstinence.	62 normal adults	More subjects had abnormally high Beck Depression Inventory scores, high scores on the trait scale of the Steate-Trait Anxiety Inventory, low vigor scores, high fatigue scores on the Profile of Mood States and moderate or severe headache on placebo than baseline (p0.05) or caffeine period ($p<0.05$). More subjects reported unauthorised use of medications during the placebo period than the caffeine period ($p=0.017$). Performance of tapping task was slower during placebo period than baseline or caffeine period ($p<0.001$).	Low to moderate caffeine consumers may experience withdrawal after caffeine consumption ceased.
Garrett Be, Griffiths RR. ***Physican dependence increases the relative reinforcing effects of caffeine versus placebo.*** Psychopharmacol 1998; 139: 195-202.	Double-blind crossover study of chronic 9-12 day **300mg/70kg/day** caffeine or placebo followed by 2 days with acute doses of caffeine 300mg/70kg or placebo and physical dependence assessed using multiple-choice procedure (receiving money or the drug again or a choice between the two drugs)	28 healthy subjects (8 males, 20 females) aged 22-40 years	Subjects maintained on chronic caffeine were willing to forfeit significantly more money and showed significant increases in withdrawal symptoms (fatigue, mood disturbance) after receiving placebo compared to the other 3 conditions. Subjects on chronic caffeine chose to receive caffeine over placebo twice as often than those maintained on chronic placebo.	Caffeine physical dependence following 300mg/day for 9-12 days increases the relative reinforcing effects of caffeine versus placebo.

APPENDIX 2

Summary of Caffeine Dose Effects

Caffeine dose and measurable physiological or toxic effects from the previous studies are summarised below. Where the published dose was quoted as mg/kg the dose was calculated for a 70kg person unless the study was undertaken in children. The negative effects are in italics.

Caffeine dose	Measurable Effect
37.5mg	dose-dependant increase in ratings of positive mood following acute intravenous doses from 37.5mg, 75mg, 150mg, 300mg (Rush et al, 1995)
40 mg	improved performance (semantic memory, focused attention, categoric search and recognition memory) and increases in alertness (Smith et al, 1999).
70mg	improvement in performance (simple reaction time task). Dose-related *decrease in hand steadiness and increase in jitteriness from 70 to 250mg* in young volunteers (Richardson et al, 1995)
90mg	decrease in maternal pulse and foetal heart rate, *increases in diastolic BP, mean arterial BP, uterine artery systolic-to-diastolic ratio, fetal heart rate accelerations and fetal aortic peak velocities* after **acute dosing** in pregnant women at 25.7 and 36.1 weeks (Miller et al, 1994)
95mg	enhanced performance on test for attention and a motor task, *increased anxiety*, decreased sluggishness following **acute dosing** in 8-12 year old children (Bernstein et al, 1994)
100mg	*prolonged sleep latency and reduced sleep efficiency and stage 4 non-REM sleep* after **single bedtime dose** (Landolt et al, 1995a). Positive dose effect for alpha and beta-EEG frequencies, anxiety, wakefulness from 1.5mg/kg, 3mg/kg and 6mg/kg and *negative dose effect for rapid information processing and BP* (Hasenfratz & Battig, 1994)
140mg	*Increase in diastolic BP, plasma epinephrine and free fatty acids* after single dose in normal volenteers (Benowitz et al, 1995)
175mg	in poor sleepers *faster heart rate, lower concentration and relaxation ratings, poorer psychomotor performance on Digital Symbol Substitution Test and greater changes in EEG activity* compared to normal sleepers (Tiffin et al, 1995)
200mg	*reduced sleep efficiency and total sleep time* in healthy men after single morning dose at 7am (Landolt et al, 1995b). *rise in blood glucose at 2, 3 and 5 hours post dose* in healthy young subjects (Pizziol et al, 1998) *Reduction in EEG spectral power density in theta and alpha ranges* in healthy males after **acute dosing** (Dimpfel et al, 1993)
210mg	*increase in whole-arm tremor*. No effect at 1mg/kg (70mg) (Miller et al, 1998). dose related *increases in ratings of anxiety and blood levels of cortisol and lactate* in normal volunteers after acute intravenous doses 3mg/kg, 5mg/kg and 7mg/kg (Nickell & Uhde, 1995-95).

230mg	*increase in ACTH release and cortisol production* in young healthy males (Lovallo et al, 1996)
	increase in systolic BP for at least 3 hours in hypertensives and normotensives and *increase in diastolic BP for 90 minutes* in normotensives *and 3 hours* in hypertensives after acute dosing (Sung BH et al, 1994)
	associated with an enhanced pressor effect in borderline hypertensives who regularly consumed ~190mg caffeine/day after a 12 hour abstinence (Pincomb et al, 1996).
	Increase in BP in borderline hypertensives especially with behavioural stress compared to normotensives following acute dosing (Lovallo & Alabsi, 1996)
250mg	decrease in HR in 1st hour, *marked diuresis and natiuresis* in first 6 hours and *increase in systolic and diastolic BP* in the older hypertensive patients (Rachima-maoz et al, 1998).
	Increase in systolic and diastolic BP, lower fatigue/inertia scores, higher vigor/activity scores, weak trend for higher scores on logical reasoning test after overnight abstinence in healthy habitual adult coffee drinkers (Phillips-Bute et al, 1998)
	Increased favourable subjective (elation, peacefulness, pleasantness) and cognitive and motor performance enhancing effects in healthy volunteers (Kaplan et al, 1997).
	Increased performance in elderly subjects, more alert, energetic and interested (Yu et al, 1991)
	Reduction in hand steadiness and headache and *increase in jitteriness* in young volunteers compared to 70mg (Richardson et al, 1995)
	Higher increases in systolic and diastolic BP in perimenopausal women before and during oestrogen therapy following acute dosing compared with premenopausal (Delrio et al, 1996)
280mg	*Increase in diastolic BP, plasma epinephrine and free fatty acids (Benowitz et al, 1995)*
300mg	associated with a *decrease in birth weight* (-1.3%) of infants born to women smokers (Cook et al, 1996)
	physical dependence demonstrated following 9-12 days **chronic caffeine dosing** (Garrett et al, 1998)
	negative mood effects following acute intravenous dose in stimulant drug abusers (Rush et al, 1995)
	poorer motor steadiness performance, increases error time and error count and a tendency to reduce maze co-ordination test performance in females (Bovim et al, 1995*)*
350mg	*Increase in mean log PC20 histamine at 150minutes and 240minutes* in mild stable asthmatics interfering with bronchial provocation test (Henderson et al, 1993)
	Prolongation of QRS duration at 90 minutes and at 3h in healthy young subjects (Donnerstein et al, 1998)
	Increase in systolic (9%) and diastolic (3%) BP in older men (Arciero et al, 1998)
	Increase in energy expenditure in younger and older men, increase in fatty acid concentrations in younger men (Arciero et al, 1995)
	Increase in cardiac contractibility lasting at least 4.5 hours in young healthy volunteers (Bender et al, 1997)
	Increase in the hypercapnic ventilatory response (Pianosi et al, 1994)

400mg	*suppression of night-time melatonin levels and attenuation in night-time temperature drop in sleep deprived subjects (Wright et al, 1997)* *decrease in simple reaction time and an increase in amplitude of late visual evoked potential on EEG (Azcona et al, 1995)*
420mg	*increase in 24 hourly urinary calcium and magnesium loss* in healthy volunteers (17-41y) (Kynast-Gales & Massey, 1994)
500mg	*increase unfavourable subjective (tension, nervousness, anxiety, excitement, irritability) and somatic effects (nausea, palpitations, restlessness) and performance disruption* in healthy volunteers (Kaplan et al, 1997) ***greater increase in BP and HR than 100mg dose* in healthy non-smoking habitual coffee drinkers (Lane et al, 1998)**
547mg	increased vigor and *mean arterial BP*, decreased fatigue and headache in chronic caffeine consumers following single dose after half day abstinence (Lane, 1997)

Abstinence or Caffeine Deprivation

200mg	Increase in serum unfilterable calcium levels, decrease three-day mean urinary calcium excretion, lower serum bone isoenzyme alkaline phosphatase after 2 week caffeine abstinence (from mean caffeine 383mg/day) in women (39-76y) taking on low calcium diet (<600mg/day) (Massey et al, 1994)
200mg-1000mg	Headache ratings higher and cheerful ratings lower after a 7 day abstinence (Richardson et al, 1995)
250mg	Decrease in systolic and diastolic BP, higher fatigue/inertia scores, lower vigor/activity scores, no effect on headache, weak trend for lower scores on logical reasoning test after overnight abstinence in healthy adult volunteers (Phillips-Bute et al, 1998) Acute ingestion of 250mg caffeine after 48h abstinence has a significant pressor effect over 120minutes in elderly normotensives. Pressor effect not significant after a 12 hour abstinence (Haigh et al, 1993).
547mg	decreased vigor and mean arterial BP, increased fatigue and headache abstinence at midday

Summary of Caffeine Concentration Effects

From the caffeine studies published since 1991 the concentration effects are summarised below. The caffeine concentrations provided in the literature were either from plasma/serum or saliva. Soto and coworkers (1994), measured caffeine levels in 12 hospitalised patients following a 300mg dose. Mean caffeine levels 1h post-dose were 5.9$\pm$2.1mcg/ml in plasma, 4.4$\pm$1.5mcg/ml in saliva and 2.9$\pm$1.1mcg/ml in CSF fluid. Correlations were 0.89 for plasma-saliva, 0.79 for saliva-CSF, and 0.77 for plasma-CSF (all $p<0.001$). Levels given as ng/ml, mcg/ml and mcg/dl were converted to mg/l.

Caffeine Levels	**Measurable Effect and/or Subjects**
0.09$\pm$0.100mg/l	Plasma pre-dose levels in young (19-26y) moderate consumers (Arciero et al, 1995)

0.12±0.04mg/l	Plasma pre-dose concentrations in older (65-80y) moderate consumers (Arciero et al, 1995)
0.5mg/l	Saliva levels **3 μmol/l** 16 hour post 200mg dose in health men lowered sleep efficiency and total sleep time (Landolt et al, 1995b).
0.66±0.16mg/l	Saliva levels 6.6±1.6mcg/dL resulted in prolongation of QRS duration at 90 minutes and at 3h in healthy young subjects (Donnerstein et al, 1998)
	Saliva levels 6.6±1.6mcg/dL resulted in increase in cardiac contractibility lasting at least 4.5 hours in young healthy volunteers (Bender et al, 1997)
0.68mg/l	Saliva levels **3.5 μmol/l** 7 hours post 100mg dose reduced sleep efficiency and stage 4 of non-REM sleep (Landolt et al, 1995a).
1.46mg/l	Saliva levels **7.5 μmol/l** 1 hour post 100mg dose prolonged sleep latency (Landolt et al, 1995a).
2.30±1.68mg/l	Plasma levels in pregnant women at booking on mean 300mg/day decrease in birth weight of infants born to smokers (Cook et al, 1996)
3.20±2.04mg/l	Plasma levels in pregnant women at 28 weeks on mean 300mg/day decrease in birth weight of infants born to smokers (Cook et al, 1996)
3.30mg/l	Saliva levels **17 μmol/l** 1 hour post 200mg dose in healthy men (Landolt et al, 1995b).
4.5mg/l	predicted peak associated with improvement in psychomotor performance (continuous attention task) for healthy elderly volunteers (Bryant et al, 1998)
4.12±2.76mg/l	Plasma levels in pregnant women at 36 weeks on mean 300mg/day decrease in birth weight of infants born to smokers (Cook et al, 1996)
5.76mg/l	2 hours post dose significant improvement in performance in elderly subjects (Yu et al, 1991)
6mg/l	associated with an enhanced pressor effect in borderline hypertensives after a 12 h abstinence in chronic caffeine consumers (Pincomb et al, 1996)
6.34±1.94mg/l	Plasma levels in younger adults who were moderate consumers post caffeine ingestion. 11% increase in energy expenditure, increase in fatty acid concentration (Arciero et al, 1995)
7.06±2.37mg/l	Plasma levels in older adults who were moderate consumers post caffeine ingestion. 9.5% increase in energy expenditure (Arciero et al, 1995)
9.0mg/l	predicted peak associated with no improvement in psychomotor performance (continuous attention task) for healthy elderly volunteers (Bryant et al, 1998)
9.10±2.01mg/l	Plasma Cmax after 400mg in young healthy males at tmax 95±29minutes led to decrease in simple reaction time and an increase in amplitudes of late visual evoked potential on EEG (Azcona et al, 1995)

Molecular weight caffeine: 194. Blood concentrations after 250mg are 0.75-6mg/l or 3-30mM (Fredholm et al, 1999)

References

Arciero PJ et al. Effects of caffeine ingestion on NE kinetics, fat oxidation, and energy expenditure in younger and older men. Am J Physiol 1995; 268:1192-8.

Arciero PJ et al. Relationship of blood pressure, heart rate and behavioural mood state to norepinephrine kinetics in younger and older men following caffeine ingestion. Europ J Clin Nutr 1998; 52:805-12.

Azcona O et al. Evaluation of the central effects of alcohol and caffeine interaction. Br J Clin Pharmacol 1995; 40:393-400.

Bender AM et al. Hemodynamic effects of acute caffeine ingestion in young adults. Am J Cardiol 1997; 79:696-9.

Benowitz NL et al. Sympathomimetic effects of paraxanthine and caffeine in humans. Clin Pharmacol Ther 1995; 58:684-91.

Bernstein GA et al. Caffeine effects on learning, performance and anxiety in normal school-age children J Am Acad Child Adolesc Psych 1994; 33:407-15.

Bovim G et al. Caffeine influence on the motor steadiness battery in neuropsychological tests. J Clin Exp Neuropsychol 1995; 17:472-6.

Bryant CA et al. Psychomotor performance: investigating the dose-response relationship for caffeine and theophylline in elderly volunteers. Eur J Clin Pharmacol 1998; 54:309-13.

Cook DG et al. Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study. Br Med J 1996; 313: 1358-62.

Couturier EG et al. Influence of caffeine and caffeine withdrawal on headache and cerebral blood flow velocities. Cephalagia 1997; 17:188-90.

Debrah K et al. Effect of acute and chronic caffeine use on the cerebrovascular, cardiovascular and hormonal responses to orthostasis in healthy volunteers. Clin Sci 1995; 89:475-80.

Delrio G et al. Increased cardiovascular response to caffeine in perimenopausal women before and during estrogen therapy. Eur J Endocrinol 1996; 135:598-603.

Dimpfel W et al. The influence of caffeine on human EEG under resting conditions and during mental loads. Clin Invest 1993;71:197-207

Donnerstein RL et al. Acute effects of caffeine ingestion on signal-averaged electrograms. Am Heart J 1998; 136:643-6.

Fotherby MD et al. Sustained caffeine use has no pressor effect in the elderly. Cardiol Elderly 1994; 2:499-503.

Fredholm BB et al. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev 1999; 51:83-133.

Garrett BE, Griffiths RR. Physican dependence increases the relative reinforcing effects of caffeine versus placebo. Psychopharmacol 1998; 139: 195-202.

Haigh RA et al. Duration of caffeine abstention influences the acute blood pressure responses to caffeine in elderly normotensives. Europ J Clin Pharmacol 1993; 44:549-53.

Hampl KF et al. Perioperative administration of caffeine tablets for prevention of postopertive headaches. Can J Anaesth 1995; 42:789-92

Hansenfratz M, Battig K. Acute dose-effect relationships of caffeine and mental performance, EEG, cardiovascular and subjective parameters. Psychopharmacol 1994; 114:281-7.

Henderson JC et al. Decrease of histamine induced bronchoconstriction by caffeine in mild asthma. Thorax 1993; 48:824-6.

James JE. Chronic effects of habitual caffeine consumption on laboratory and ambulatory blood pressure levels. J Cardiovasc Risk 1994; 1:159-64.

Kaplan GB et al. Dose-dependent pharmaco-kinetics and psychomotor effects of caffeine in humans. J Clin Pharmacol 1997; 37:693-703.

Kynast-Gales SA, Massey LK. Effect of caffeine on circadian excretion of urinary calcium. J Am Coll Nut 1994; 15:467-72

Landolt HP et al. Caffeine intake (200mg) in the morning affects human sleep and EEG power spectra at night. Brain Res 1995; 675:67-74.

Landolt HP et al. Caffeine reduces low-frequency delta activity in the human sleep EEG. Neuropsychopharmacol 1995; 12:229-38.

Lane JD et al. Caffeine raises blood pressure at work. Psychosomatic Med 1998; 60:327-30.

Lane JD. Effects of brief caffeinated-beverage deprivation on mood, symptoms, and psychomotor performance. Pharmacol Biochem Behav 1997; 58:203-8.

Lovallo WR et al. Stress-like adenocorticotropin responses to caffeine in young healthy men. Pharmacol, Biochem Behav 1996; 55:365-9.

Lovallo WR, Alabsi M. Caffeine and behavioural stress effects on blood pressure in borderline hypertensive caucasian men. Health Psychol 1996; 15:11-17.

Lovallo WR et al. Hypertension risk and caffeine's effect on cardiovascular activity during mental stress in young men. Health Psychol 1991: 10:236-43.

MacDonald TM et al. Caffeine restriction: effect on mild hypertension. Br Med J 1991; 303:1235-8.
Massey LK et al. Interactions between dietary caffeine and calcium on calcium and bone metabolism in women. J Am Coll Nutr 1994; 13: 592-6.

Miller RC et al. Acute maternal and fetal cardiovascular effects of caffeine. Am J Perinatol 1994; 11:132-6.

Miller LS et al. Caffeine but not time of day, increases whole arm physiological tremor in non-smoking moderate users. Clin Exp Pharmacol Physiol 1998; 25:131-3.

Myers MG , Reeves RA. The effect of caffeine on daytime ambulatory blood pressure. Am J Hyperten 1991; 4:427-31.

Newby DE et al. Caffeine restriction has no role in the management of patients with symptomatic idiopathic ventricular premature beats. Heart 1996; 76:355-7.

NickeLL PV, Uhde TW. Dose-response effects of intravenous caffeine in normal volunteers. Anxiety 1994-95; 1:161-8.

Phillips-Bute BG & Lane JD. Caffeine withdrawal symptoms following brief caffeine deprivation. Physiol Behav 1997; 63:35-39

Pianosi P et al. Effect of caffeine on the ventilatory response to inhaled carbon dioxide. Resp Physiol 1994; 95:311-20.

Pincomb GA et al. Acute blood pressure elevations with caffeine in men with borderline systemic hypertension. Am J Cardiol 1996; 77:270-74.

Pizziol A et al. Effects of caffeine on glucose tolerance: a placebo controlled study. Europ J Clin Nurtr 1998; 52:846-9.

Rachima-maoz C et al. The effect of caffeine on ambulatory blood pressure in hypertensive patients. Am J Hyperten 1998; 11:1426-32

Richardson NJ et al. Mood and performance effects of caffeine in relation to acute and chronic caffeine deprivation. Pharmacol Biochem Behav 1995; 52:313-20.

Romagnoli C et al. Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants. Therapeutic Drug Monit 1992; 14:14-9.

Rush CR et al. Intravenous caffeine in stimulant drug abusers: subjective reports and physiological effects. J Pharmacol Exp Ther 1995; 273:351-8

Silverman K, Griffiths RR. Low-dose caffeine discrimination and self-reported mood effects in normal volunteers. J Exp Anal Behav 1992; 57:91-107.

Silverman K et al. Withdrawal syndrome after the double-blind cessation of caffeine consumption. N Engl J Med 1992; 327:1109-14.

Smith AP, Sturgess W and Gallagher J. Effects of a low dose of caffeine given in different drinks on mood and performance. Human Psychopharmacology, 14, 473-482.

Soto J et al. Cerebrospinal fluid concentrations of caffeine following oral drug administration: correlation with salivary and plasma concentrations. Ther Drug Monit 1994; 16:108-10.

Sung BH et al. Prolonged increases in blood pressure by a single oral dose of caffeine in mildly hypertensive men. Am J Hyperten 1994; 7:755-8.

Tiffin P et al. Pharmacokinetic and pharmacodynamic responses to caffeine in poor and normal sleepers. Psychopharmacol 1995; 121:494-502.

Wright KP Jr et al. Caffeine and light effects on nighttime melatonin and temperature levels in sleep-deprived humans. Brain Res 1997; 747: 78-84.

Yu G et al. A comparison of the central nervous system effects of caffeine and theophylline in elderly subjects. Br J Clin Pharmacol 1991; 32:341-5.

Safety Aspects of Dietary Caffeine: A Commentary on the Final Report of the ANZFA Expert Working Group on Caffeine

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This document is intended for distribution with the
Final Report of the ANZFA Expert Working Group on Caffeine

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Executive Summary
This report is a commentary on the *Final Report* of the ANZFA Expert Working Group on Caffeine. Although a Member of the Working Group and a contributor throughout the protracted period of the Group's deliberations, the present author declined co-authorship of the *Final Report* for reasons of professional integrity. It is this author's opinion, based on extensive familiarity with the relevant scientific literature, that the contents of the *Final Report* are potentially harmful to the public interest. Accordingly, it is intended that this commentary, which reflects the author's individual deliberations, be distributed as an essential supplement to the *Final Report*.

Cardiovascular Health and Term of Reference C
The Final Report provides an inadequate and misleading account of current scientific knowledge concerning the effects of dietary caffeine on cardiovascular health. Conclusions contained in *Section C2.0 Cardiovascular effects of caffeine* indicate poor understanding of the experimental and epidemiological evidence on the cardiovascular effects of caffeine. It may be confidently concluded that any extension of the use of caffeine in soft drinks will create quantifiable harm to the long-term cardiovascular health of consumers, a large proportion of whom are likely to be children.

Miscellaneous Comments and Terms of Reference A and B

- The *Final Report* is confused in relation to Term of Reference A. At one point, it is stated that there 'appears to be evidence of a "no effect" level', whereas mention is made later of 'the threshold dose'. If there is no identifiable level at which effects are absent, then there can be no threshold.

- Insufficient attention is given in the *Final Report* to the available evidence showing the harmful behavioural effects in adult and child caffeine consumers during brief periods of abstinence (caffeine-withdrawal effect).

- Caffeine-withdrawal syndrome is a well established phenomenon, the symptoms of which include headache, mood disturbance and fatigue.

- Regarding Term of Reference B, it is reasonable to speak of caffeine as 'addictive', because repeated use produces physical dependence.

- Contrary to the impression given in the *Final Report*, well-controlled studies continue to implicate maternal caffeine use as a cause of adverse pregnancy outcomes.

- Contrary to the impression given in the *Final Report*, there is every reason to believe that the harmful effects of dietary caffeine in adults extrapolate to children.

Conclusions

- Habitual use of caffeine leads to *physical dependence* (as evidenced by the existence of a well characterised abstinence-induced 'withdrawal syndrome').
- Habitual use has *no demonstrated benefits*.

- Dietary caffeine has *harmful physical and behavioural effects.*
- The harmful effects of caffeine *probably extrapolate to children*.

This report is a commentary on the *Final Report* of the ANZFA Expert Working Group on Caffeine (Chair: Dr Alex Proudfoot). Although a Member of the Working Group and a contributor throughout the protracted period of the Group's deliberations, the present author declined co-authorship of the *Final Report*. My reasons for declining authorship arouse in a particular context, which I believe should be explained. Consequently, this report is in two parts: Part 1 comments on operational aspects of the Expert Working Group, and Part 2 comments on the content of the Working Group's *Final Report*.

Part 1: Operation of the Working Group

Following receipt of initial correspondence from Dr Glen Stanley, regarding an application received by ANZFA to extend the use of caffeine in soft drinks, I indicated in a reply dated 3 February 1998 that I was of the opinion that the available evidence recommended against any extension of the use of caffeine on public health and safety grounds. Subsequent intermittent correspondence followed, and I was invited to become a member of the Expert Working Group on Caffeine. While the Expert Group was guided by specific terms of reference, operational details were never clarified. In due course, written comments were requested and teleconferences were arranged on an essentially *ad hoc* basis.

The absence of more formal procedures had unfortunate consequences for my involvement in the process. It was not until the last of the teleconferences (14 march 2000) that I learned of the Chair's intention to incorporate individual written submissions into a single *'co-authored'* document. Prior to this, I had assumed that the diversity of views that had emerged in the Group's deliberations would be preserved in a final document authored by ANZFA staff. The issue, however, was put beyond debate and the Group was informed that all members were expected to be co-authors (i.e., co-signatories) of a final document purporting to represent a consensual view. For me, this new and surprising state of affairs created a dilemma. Information in the public domain indicates that at least one member of the Expert Group, Professor Andrew Smith, has a record of research funding provided by caffeine industry sources. Indeed, the *Final Report* shows Professor Smith as having been nominated for membership of the Working Group by the Australasian Soft Drink Association. Moreover, literature distributed by commercial outlets of the caffeine industry explicitly cite Professor Smith as the source of findings which purport to show that caffeine is beneficial to humans. Such opinions are diametrically opposed to my interpretation of the research evidence.

These facts have a direct bearing on matters of professional ethics and integrity. The issues at stake are not unique to caffeine. For example, the Australian National Health and Medical Research Council (NHMRC) discourages Australian scientists from accepting funds for research (for any purpose) emanating from the tobacco industry. The NHMRC takes the position that tobacco products are damaging to health and scientists who accept tobacco industry funds are banned from receiving research support from the NHMRC. The ban may extend to include any institution with which such a scientist is affiliated. The ethical considerations which led the NHMRC to take this stand in relation to tobacco-sponsored research are identical to the ethical considerations that press upon me in relation to caffeine research. The general scientific community now believes and accepts that tobacco products are harmful to

health. The NHMRC is committed to lessening disease and promoting health. Accordingly, that body expressly and publicly seeks to dissociate itself from any direct or indirect collaboration with the tobacco industry. My position is identical in relation to the caffeine industry. My considered scientific opinion is that long-term use of caffeine is harmful. I would therefore not wish myself to be professionally associated, either directly or indirectly, with persons or parties whose actions have given, or may give, support to the purveyors of caffeine products.

In light of the above, I expressed the wish to submit an independent report, an option that had been mentioned on a number of occasions by the Working Group Chair. Under the circumstances, an independent report was the only means left open to me of ensuring my complete independence from a process that could have involved, or could be seen to have involved, collaboration with caffeine industry activities.

Part 2: Comments on the Final Report of the ANZFA Expert Working Group on Caffeine

At the outset, I feel compelled to express my opinion that the contents of the, *Final Report of the ANZFA Expert Working Group on Caffeine* are potentially harmful to the public interest. I base this opinion on extensive familiarity with the relevant scientific literature. I have conducted original scientific research on the effects of caffeine over a period of almost two decades and have published widely on the subject in refereed scientific journals. I have also published extensive reviews of the research of other scientists, including two books, *Caffeine and Health* (1991, London: Academic Press) and *Understanding Caffeine: A Biobehavioral Analysis* (1997a, Thousand Oaks, CA: Sage Publications). The kernel of my criticism of the *Final Report* is that although sections of it provide good technical information and sound scientific opinion, these are combined with sections containing exceedingly poor accounts of current scientific knowledge. This juxtaposition of good and bad science, undermines any constructive contribution the *Report* could have had, while giving credence to highly spurious and potentially harmful conclusions contained in the *Report*. The problem is compounded by the fact that the strongest sections of the *Report* concern the *basic* science of caffeine (e.g., pharmacokinetics, metabolism, mechanisms of actions) that relate only somewhat indirectly to *clinical* outcomes. Consequently, there is a risk that conclusions in the report, which relate most directly to important health outcomes, may be wrongly perceived to be well-founded simply by association with the genuinely well-founded sections of the *Report*. Indeed, it is imperative to the integrity of the overall deliberations of the Working Group, that the present document, which is critical of the *Final Report*, be distributed as an **essential supplement** to the *Final Report*.

Cardiovascular Health and Term of Reference C

The main criticisms contained herein relate to sections in the *Final Report* that deal with Term of Reference C. In addition to specific criticisms relating to interpretations of the scientific literature, criticism may also be levelled at the 'tone' adopted in the *Final Report*. There are examples of bias throughout the document and some attempt is made to instance these below. Particular concerns are raised in relation to *Section C2.0 Cardiovascular effects of caffeine*. In commenting on this section, I should point

out that while having wide-ranging scientific interests in the effects of caffeine, I have special expertise in relation to caffeine and cardiovascular health. In my opinion, *Section C2.0* of the *Final Report* provides an inadequate and misleading account of current scientific knowledge regarding the effects of dietary caffeine on cardiovascular health.

Acute and chronic effects on blood pressure: Experimental studies. The first sentence of *Section C2.1 Acute effects of caffeine on blood pressure and tolerance* claims that 'high doses of caffeine have been reported to produce . . . increases in blood pressure'. This is misleading, because it suggests that such effects are limited to 'high doses'. However, there is extensive evidence showing that the hypertensive effects of caffeine are not restricted to high doses, but are also evident following ingestion of 'moderate' amounts typical of the consumption patterns of countless 'average' consumers. The same section incorrectly concludes that 'the effect of low doses of caffeine has not been accurately measured'. The exact opposite is true. The finding that caffeine elevates blood pressure, even at low doses (as defined in the *Final Report* to mean 'intakes in the range of 80-250 mg of caffeine') has been established beyond doubt, being one of the most reliable findings in the scientific literature on the human effects of caffeine. This finding is well documented in the literature that was at the disposal of the Expert Working Group. One of the more extensive and detailed accounts of the effects of caffeine on blood pressure is provided in Chapter 5 of *Caffeine and Health* (James, 1991), which contains over 140 scientific references relevant to the topic. Further consideration and an update of this literature is provided in *Understanding Caffeine: A Biobehavioral Analysis* (James, 1997a), which again shows that caffeine elevates blood pressure, even at low doses. Some more recent references include Shepard et al. (2000), Lane et al. (1998), and Rachima-Maoz et al. (1998).

Section C2.1 also misrepresents the situation concerning studies which have specifically examined whether habitual use of caffeine leads to the development of tolerance to its hypertensive effects. Only one study is cited as finding that tolerance develops incompletely. Indeed, there are several lines of evidence which converge to strongly suggest that habitual consumers do not develop complete tolerance to caffeine (i.e., the drug continues to elevated blood pressure even after prolonged use). Strong inferential indications that habitual consumers are not immune to the blood pressure elevating effects of caffeine is provided by the large number of individual studies designed to investigate reactivity to acute caffeine challenge. In an analysis of 38 such studies, James (1997a) found that the participants represented the entire spectrum of caffeine users, ranging from non-users to consumers of higher than average amounts. Despite the overall similarity of method (caffeine challenge after a brief period of caffeine abstinence), no systematic differences in consumer-associated reactivity to caffeine were evident in the overall results. Moreover, in the minority of studies in which caffeine consumer status was used as an explicit criterion for selecting participants representing "high" and "low" habitual consumers, no systematic differences in caffeine reactivity were observed between the different user groups (e.g., James, 1990; Lane et al., 1990).

Of more direct relevance to the question of hemodynamic tolerance, a few studies have examined the effects of repeated caffeine doses, rather than employing a single caffeine dose (characteristic of the large majority of experimental studies). It has been

found that the magnitude of caffeine-induced pressor effects is inversely related to plasma caffeine concentration at the time the drug is ingested, irrespective of prior history of use (Smits et al., 1985). Consequently, a second cup of coffee, for example, ingested within one or two hours of an earlier cup, produces a discernible, but smaller, pressor effect than that caused by the first cup (Goldstein et al., 1990; Lane & Manus, 1989; Ratliff-Cain et al., 1989). As plasma levels fall, the hemodynamic effects of the drug increase, in both consumers and non-consumers alike (Smits et al., 1985). Of the various factors that influence plasma caffeine level, elimination half-life and time since the drug was last consumed are generally the main determinants. Given that the half-life of caffeine in humans is typically about five hours (Pfeifer & Notari, 1988), and that the drug is usually consumed in separate portions throughout the day (with fewer portions consumed later in the day followed by overnight abstinence), plasma caffeine concentration is typically highest in the late afternoon and lowest on awakening in the morning (Denaro et al., 1991; Lelo et al., 1986). Overnight abstinence of 10-12 hours is characteristic of the consumption patterns of the majority of consumers, and leads to almost complete depletion of systemic caffeine by early morning (Lelo et al., 1986; Pfeifer & Notari, 1988; Shi et al., 1993b). This, in turn, renders the consumer sensitive to the hemodynamic effects of the drug when re-exposure next occurs (typically, shortly after awakening) (Denaro et al., 1991; Shi et al., 1993a; Smits et al., 1985). That is, to a substantial and important degree, habitual consumers of low doses of caffeine do *not* develop tolerance to the blood pressure elevating effects of the drug.

Among the comparatively few studies that have directly examined the effects of caffeine exposure resembling usual dietary patterns of consumption, there is evidence that modest sustained decreases in blood pressure occur when caffeine beverages are either removed from the diet (Bak & Grobbee, 1990) or are replaced by decaffeinated alternatives (van Dusseldorp et al., 1989). Similar results have been obtained in a number of studies in which ambulatory monitoring was used to measure blood pressure level for extended periods. Of seven such studies, four reported persistent caffeine-induced increases in blood effects (Green & Suls, 1996; James, 1994; Jeong & Dimsdale, 1990; Superko et al., 1994) and three reported no effect (Eggertsen et al., 1993; MacDonald et al., 1991; Myers & Reeves, 1991). Importantly, the seven studies are distinguishable on the basis of the length of the time epochs used to analyse results. Readings were averaged across shorter time periods in the four positive studies, and longer time periods in the three negative studies. Since the hemodynamic effects of caffeine generally peak within about one hour post-ingestion, and are substantially diminished within about 3 hours (Robertson et al., 1978), blood pressure increases appear to have been obscured in the three negative studies because readings were averaged across inappropriately long epochs. In the study by James (1994) ambulatory blood pressure was measured over 24-hour periods in participants who were maintained on a regimen of low-dose caffeine intake. Blood pressure levels, when averaged over relatively short epochs, correlated very well with systemic caffeine levels. Caffeine-induced increases in blood pressure peaked at 6 mm Hg systolic and 5 mm Hg diastolic by late morning, and increases persisted throughout the day. The study provided a clear demonstration of the blood pressure elevating effects of dietary caffeine in 'average' consumers. Moreover, the participants were mostly adolescents and young adults, and as such the results of the study are probably generalisable to younger adolescents.

Chronic effects of caffeine and blood pressure: Epidemiological studies. *Sections C2.2* to *C5* of the *Final Report* purport to deal with the chronic effects of habitual caffeine use. In fact, these sections demonstrate a profound failure to appreciate the importance of experimental evidence (outlined above) in determining the long-term implications of caffeine use for cardiovascular health. Moreover, as an account of the relevant epidemiological literature, *Sections C2.2* to *C4* are grossly inadequate. *Section CS.2* states that the 'longer term effects of caffeine on blood pressure have been studied in several large epidemiological studies [and that] five such studies have been published since 1990'. Since the first large epidemiological study of caffeine and cardiovascular disease was conducted almost 40 years ago, more than 100 have been published to date. Of these, about 20 have specifically considered the epidemiology of caffeine and blood pressure. The assertion that only 'five such studies have been published' over the past decade is especially remarkable in light of the fact that the Working Group had before it the contents of the relevant chapter from *Understanding Caffeine: A Biobehavioral Analysis* (James, 1997a), which lists (p. 83) seven such studies for the first half of the decade alone. In fact, the five studies presented in the *Final Report* represent a biased selection of studies. An even more extreme selection bias is evident in *Section C2.3.* Again, only five studies are identified as being relevant, which represents a small fraction of the actual number published. Again, more than 100 such studies are cited by James (1991, 1997a), and at least 30 have been published over the past decade. The inclusion of an unpublished report in *Section C2.5* can only strengthen the charge of bias in the *Final Report*. With an abundance of published literature available, the question arises as to why it was necessary to resort to the inclusion of an unpublished report, the details of which are not available to the reader for independent scrutiny. The impression is created that the unpublished report was included to bolster (albeit feebly) preconceived conclusions.

More comprehensive perusal of the literature indicates that of 18 large epidemiological studies of caffeine and blood pressure, which are readily available in the published literature, five reported no association (Bertrand et al., 1978; Dawber et al., 1974; Lancaster et al., 1994; Medeiros, 1982; Stanton et al., 1978), six reported a significant positive association for either systolic or diastolic blood pressure (Birkett & Logan, 1988; Burke et al., 1992; Lang et al., 1983; Lang, Degoulet et al., 1983; Miner et al., 1985; Shirlow et al., 1988), and seven reported an inverse association (Gyntelberg et al., 1995; Kirchhoff et al., 1994; Lewis et al., 1993; Periti et al., 1987; Salvaggio et al., 1990; Salvaggio et al., 1992; Stensvold et al., 1989). This diversity of outcomes has led some commentators to feel unable to draw conclusions from the epidemiological evidence. However, rational conclusions are possible when the epidemiological findings are integrated with the experimental results, as good science demands. Specifically, the apparent inconsistencies concerning the association between caffeine consumption and population blood pressure can be understood as an artefact arising from the general failure of epidemiological studies to take account of participants' systemic caffeine levels at the time of blood pressure measurement. The experimental findings show that habitual consumers frequently experience a modest decrease in blood pressure during periods of caffeine abstinence (James, 1994, 1997b). In this regard, it is important to note that the epidemiological studies typically have not reported (and no doubt did not record) the time since caffeine was last consumed prior to blood pressure being measured. One study which did not share this widespread methodological flaw found that participants who reported consuming caffeine during the three hours prior to examination had significantly elevated blood

pressure compared to those who had consumed no caffeine during the same period (Shirlow et al., 1988).

It therefore appears that the observed (i.e., population) association between caffeine and blood pressure depends upon the distribution of caffeine consumers who happen to be caffeine-sated versus caffeine-withdrawn at the time of examination. In epidemiological studies of caffeine and blood pressure, it is typical for participants to be asked to report the amount of caffeine they consume and for a single measurement of blood pressure to be taken. However, the relationship between caffeine and blood pressure depends on level of habitual usage **and** the time elapsed between the most recent intake of caffeine and the moment at which blood pressure is measured. Irrespective of habitual use, recent caffeine consumption will generally increase blood pressure (positive association). Conversely, in habitual consumers, blood pressure is likely to be 'unaffected' after a relatively brief period of abstinence (null result), or decreased after a longer period (10 or more hours) of abstinence (inverse association).

Epidemiological studies that have reported an inverse association between caffeine and blood pressure, measured blood pressure after periods of abstinence capable of inducing reductions in blood pressure. Rather than indicating a protective effect (as has been suggested), the inverse association reported in these studies is consistent with caffeine having potentially damaging elevating effects on blood pressure during normal periods of caffeine consumption. This phenomenon, whereby blood pressure in habitual consumers either increases or decreases, depending upon when the drug was last ingested, is not unique to caffeine. A similar pattern has been identified for cigarette smoking and population blood pressure. Although it is generally accepted that smoking increases blood pressure, epidemiological studies have failed to show a sustained effect, apparently because in most studies blood pressure measurements have been taken after the smokers had been abstinent from smoking for periods long enough to produce nicotine-withdrawal decreases in blood pressure (Pickering et al., 1991).

In conclusion, comments contained in *Section C2.0 Cardiovascular effects of caffeine* indicate poor understanding of the experimental and epidemiological evidence on the cardiovascular effects of caffeine. *Section C2.0* contains a biased selection of literature which is perfunctorily reviewed. More detailed analysis of the accumulated experimental and epidemiological evidence indicates that dietary caffeine is a cardiovascular risk factor. With regard to blood pressure specifically, if it is assumed that (a) dietary caffeine has the effect of elevating average population blood pressure by 2-4 mm Hg, a reasonable inference considering the available experimental data (e.g., James, 1994; Jeong & Dimsdale, 1990; Superko et al., 1994) and (b) habitual consumers comprise 80% or more of the population, then extrapolation based on epidemiological blood pressure data (MacMahon et al., 1990; Rodgers & MacMahon, 1999) suggests that population-wide cessation of caffeine use could lead to 9-14% less coronary heart disease and 17-24% less stroke (James, 1997b). Thus, there is no foundation for the conclusion in the *Final Report* (Executive Summary and Conclusions relating to Term of Reference C) that there is 'little evidence that caffeine in typical dosages consumed in the diet contributes to hypertensive disease'. On the contrary, with regard to Term of Reference C, it may be confidently concluded that any extension of the use of caffeine in soft drinks represents an identifiable and

quantifiable hazard to consumers, a large proportion of whom are likely to be children.

Miscellaneous Comments and Terms of Reference A and B

Passages in the *Final Report* are identified by section number rather than page number, because the draft report in my possession may not be the final draft.

- The *Final Report* is inconsistent in its conclusions regarding Term of Reference A (Executive Summary and the Conclusions). At one point, it is correctly stated that there 'appears to be evidence of a "no effect" level'. Then, a few passages later reference is made to 'the threshold dose'. If there is no identifiable level at which effects are absent, then there can be no threshold.

- Various sections of the *Final Report* refer to the large literature which purports to show that caffeine is beneficial to aspects of human performance. Mention is made in the *Final Report* of the contrary view that the reputed 'benefits' are illusory, but the *Report* gives insufficient attention to this question. The illusion of benefits occurs because most participants in caffeine experiments are caffeine consumers who are in a state of mild caffeine deprivation when they arrive at the experimental laboratory. This relative state of caffeine deprivation, which harms performance (e.g., James, 1998; Rogers & Dernoncourt, 1998), is reversed following subsequent ingestion of caffeine and performance may improve. That is, poor experimental method has led to the widespread belief that caffeine enhances performance. Where adequate experimental controls have been employed, putative 'benefits' have been shown to be the result of a reversal of caffeine deprivation. After ingesting caffeine, habitual consumers show no absolute benefits, they merely perform better than when they were caffeine deprived. It is the harmful effects of caffeine deprivation that has created the illusion (to consumers and gullible experimenters alike) that caffeine is beneficial. While the *Final Report* mentions the caffeine-deprivation hypothesis, it does not do justice to the strength of the argument nor the extent of the empirical evidence in support of the hypothesis. Only two studies are mentioned (James, 1998; Rogers & Dernoncourt, 1998), but others are available (e.g., Jones et al., 2000; Lane & Phillips-Bute, 1998; Rizzo et al., 1988; Silverman et al., 1992; Robelin & Rogers, 1998). Of particular relevance is a study involving school children whose diet included caffeine (Berstein et al., 1998). Following removal of caffeine from their diet, the children showed a significant deterioration in performance and attention. Degraded performance continued for a week before recovering (caffeine-deprivation effect).

- The first sentence of *Point (4)* under *Section A2.1.3 Summary of effects of caffeine at low doses* asserts, 'In contrast to the effects of caffeine consumption, withdrawal of caffeine has few effects on performance'. This statement is untrue. As stated in the preceding paragraph, until recently, experimental studies to test these effects had not been performed. As mentioned above, according to current evidence, which is substantial and accumulating, caffeine deprivation harms performance. The second sentence of *Point (4),* states that the withdrawal effects of caffeine 'may largely reflect the expectancies of the volunteers and the failure to conduct "blind" studies'.

This is a complete misrepresentation of the scientific evidence. Particular weight is given, under *Section B1.1 Withdrawal Symptoms*, to the telephone survey conducted by Dews et al. (1999), which concluded that few effects were attributed by respondents to caffeine withdrawal - a finding that stands in stark contrast to most of the large literature on caffeine withdrawal. It may be of some interest to note that information in the public domain shows that the principal author of the aforementioned study, Professor Peter Dews, has a long history of collaboration with caffeine industry bodies.

> As for the existence of the phenomenon of caffeine withdrawal, it is categorically beyond doubt. All the major reviews of the relevant literature attest to the existence of the phenomenon (e.g., Griffiths & Mumford, 1995a, b; Heishman & Henningfield, 1992; James, 1991, 1997a; Strain et al. 1994). The phenomenon is well-characterised and includes headache, mood disturbance and fatigue (e.g., Evans & Griffiths, 1999; Garrett & Griffiths, 1998; Jones et al., 2000). Although most research to date has involved adult consumers, studies also confirm the existence of adverse withdrawal effects associated with dietary caffeine in children (Hughes & Hale, 1998). Indeed, the phenomenon of caffeine withdrawal is so well-established that specialist sub-fields have emerged to study particular aspects. For example, it is now recognised that caffeine-withdrawal induced postdural puncture headache is frequently experienced by patients following lumbar puncture for clinical diagnostic purposes and following spinal anesthesia (e.g., Morewood, 1993; Hampl et al., 1995; Weber et al., 1993). That such headaches are indeed induced by caffeine withdrawal is confirmed by the fact that prophylactic administration of caffeine provides a simple and effective remedy (e.g., Yucel et al., 1999).

- Regarding Term of Reference B, it is reasonable to speak of caffeine as 'addictive'. While acknowledging that the term might best be avoided, because its use is frequently vague and emotive, it appears that many people use the term as a synonym for 'physical dependence'. As such, caffeine may be regarded as a drug of addiction.

- The second sentence in the second paragraph under *Section A2.3 Interpretation of effects* was contributed by this author in a different context. To be accurate in the present context, it should include the phrase 'any more or less sensitive' (rather than simply 'any more sensitive'). The same sentence appears again in the Conclusions under *A3.3 Effects of low doses of caffeine in children*.

- *Section C1.1Effects on the foetus, pregnancy and reproductive parameters* makes the unfounded statement that 'Confounding by other factors such as maternal smoking, alcohol or parity provide an alternative explanation' of the findings of a host of studies that implicate dietary caffeine during pregnancy as a factor contributing to lower birth weight and increased risk of spontaneous abortion. In reality, control of confounders is a standard operation in epidemiological research on caffeine. Very few studies fail to control extensively for the possible influence of confounders. Indeed, it can be argued reasonably that many studies have 'over controlled' for confounders. That is,

studies frequently attribute effects to smoking and alcohol, which may actually have been due to caffeine. Even in such studies, caffeine has frequently been found to contribute additional harm in relation to pregnancy outcomes (see James 1984, 1991, 1997a for reviews). Thus, contrary to the impression given in the *Final Report*, well-controlled studies continue to implicate caffeine as a contributor to adverse pregnancy outcomes (e.g., Eskenazi et al., 1999; Fernandes et al., 1998)).

- The final *Section C4.1* under *C4.0 Overall conclusions* asserts 'It would appear that a *precise* link between caffeine contributing to cardiovascular disease has not been established'. Such terminology adds to the overall appearance of bias. For example, almost no one disputes that cigarette smoking contributes to cardiovascular disease, but many experts would admit that a 'precise link' has yet to be established. Section C4.2 asserts that 'it is not possible to conclude' either that caffeine consumption may be harmful to health in children or that the known adverse effects in adults extrapolate to children. On the contrary, there is very substantial evidence that caffeine is harmful to adults and there is every reason to believe that children are likely to be susceptible to many of the same effects.

- The two appendices add little of value to the *Final Report*. Indeed, they further undermine the credibility of the *Report*. The inclusion of the appendices has the appearance of attempting to convey thoroughness and rigor. However, in the absence of scholarly analysis, the laborious tabulation and listing of references conveys no additional understanding of the issues under consideration. It is essentially pretentious.

Conclusions

Drawing on two decades of research on the effects of caffeine in humans, the present author is led to the following conclusions:

- Habitual use of caffeine leads to *physical dependence* (as evidenced by the existence of a well characterised abstinence-induced 'withdrawal syndrome').

- Habitual use has *no demonstrated benefits*.

- Dietary caffeine has *harmful physical and behavioural effects.*

- The harmful effects of caffeine *probably extrapolate to children*.

Finally, despite having been advised by the Chair of the Expert Working Group not to offer an opinion in relation to the application currently under consideration, I believe I have a professional responsibility to put my opinion about this important subject on the public record. Accordingly, I strongly recommend that the application currently before ANZFA to extend the use of caffeine in non-alcoholic beverages be unconditionally denied.

References

Bak, A. A., & Grobbee, D. E. (1990). A randomized study on coffee and blood pressure. *Journal of Human Hypertension*, **4**, 259-264.

Bernstein, G. A., Carroll, M. E., Dean, N. W. and Crosby, R. D. (1998). Caffeine withdrawal in normal school-age children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 37, 858-65.

Bertrand, C. A., Pomper, I., Hillman, G., Duffy, J. C., & Michell, I. (1978). No relation between coffee and blood pressure. *New England Journal of Medicine*, **299**, 315-316.

Birkett, N. J., & Logan, A. G. (1988). Caffeine-containing beverages and the prevalence of hypertension. *Journal of Hypertension Suppl*., **6**, S620-S622.

Burke, V., Beilin, L. J., German, R., Grosskopf, S., Ritchie, J., Puddey, I. B., & Rogers, P. (1992). Association of lifestyle and personality characteristics with blood pressure and hypertension: a cross-sectional study in the elderly. *Journal of Clinical Epidemiology*, **45**, 1061-1070.

Dawber, T. R., Kannel, W. B., & Gordon, T. (1974). Coffee and cardiovascular disease: Observations from the Framingham study. *New England Journal of Medicine*, **291**, 871-874.

Denaro, C. P., Brown, C. R., Jacob, P. I., & Benowitz, N. L. (1991). Effects of caffeine with repeated dosing. *European Journal of Clinical Pharmacology*, **40**, 273-278.

Dews, P. B., Curtis, G. L., Hanford, K. L., and O'Brien, C. P. (1999). The frequency of caffeine withdrawal in a population-based survey and in a controlled, blinded pilot experiment. *Journal of Clinical Pharmacology*, **39**, 1221-32.

Eggertsen, R., Andreasson, A., Hedner, T., Karlberg, B. E., & Hansson, L. (1993). Effect of coffee on ambulatory blood pressure in patients with treated hypertension. *Journal of Internal Medicine*, **233**, 351-355.

Eskenazi, B., Stapleton, A. L., Kharrazi, M., and Chee, W. Y. (1999). Associations between maternal decaffeinated and caffeinated coffee consumption and fetal growth and gestational duration. *Epidemiology*, **10**, 242-9.

Evans, S. M., and Griffiths, R. R. (1999). Caffeine withdrawal: a parametric analysis of caffeine dosing conditions. *Journal of Pharmacology & Experimental Therapeutics*, **289**, 285-94.

Fernandes, O., Sabharwal, M., Smiley, T., Pasturszak, A., Koren, G., and Einarson, T. (1998). Moderate to heavy caffeine consumption during pregnancy and

relationship to spontaneous abortion and abnormal fetal growth: A meta-analysis. *Reproductive Toxicology*, **12**, 435-444.

Garrett, B. E., and Griffiths, R. R. (1998). Physical dependence increases the relative reinforcing effects of caffeine versus placebo. *Psychopharmacology*, **139**, 195-202.

Goldstein, I. B., Shapiro, D., Hui, K. K., & Yu, J. L. (1990). Blood pressure response to the "second cup of coffee". *Psychosomatic Medicine*, **52**, 337-345.

Green, P. J., & Suls, J. (1996). The effects of caffeine on ambulatory blood pressure, heart rate, and mood in coffee drinkers. *Journal of Behavioral Medicine*, **19**, 111-128.

Griffiths, R. R., & Mumford, G. K. (1995a). Caffeine reinforcement, discrimination, tolerance and physical dependence in laboratory animals and humans. In C. R. Schuster, S. W. Gust, & M. J. Kuhar (Eds.), *Pharmacological aspects of drug dependence--Toward an integrated neurobehavioral approach--Handbook of Experimental Pharmacology* (pp. in press). New York: Springer-Verlag.

Griffiths, R. R., & Mumford, G. K. (1995b). Caffeine--a drug of abuse? In F. E. Bloom & D. J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress* New York: Raven Press.

Gyntelberg, F., Hein, H. O., Suadicani, P., & Sorensen, H. (1995). Coffee consumption and risk of ischaemic heart disease--a settled issue? *Journal of Internal Medicine*, **237**, 55-61.

Hampl, K. F., Schneider, M. C., Ruttimann, U., Ummenhofer, W., & Drewe, J. (1995). Perioperative administration of caffeine tablets for prevention of postoperative headaches. *Canadian Journal of Anaesthesia*, **42**, 789-792.

Heishman, S. J., & Henningfield, J. E. (1992). Stimulus functions of caffeine in humans: relation to dependence potential. *Neuroscience and Biobehavioral Reviews*, **16**, 273-287.

Hughes, J. R. and Hale, K. L. (1998). Behavioral effects of caffeine and other methylxanthines on children. *Experimental and Clinical Psychopharmacology*, **6**, 87-95.

James, J. E. (1990). The influence of user status and anxious disposition on the hypertensive effects of caffeine. *International Journal of Psychophysiology*, **10**, 171-179.

James, J. E. (1991). *Caffeine and Health*. London: Academic Press.

James, J. E. (1994). Chronic effects of habitual caffeine consumption on laboratory and ambulatory blood pressure levels. *Journal of Cardiovascular Research*, **1**,

159-164.

James, J. E. (1997a). *Understanding Caffeine: A Biobehavioral Analysis*. Thousand Oaks, CA: Sage Publications.

James, J. E. (1997b). Caffeine and blood pressure: Habitual use is a preventable cardiovascular risk factor. *The Lancet*, 349, 279-281.

James, J. E. (1998). Acute and chronic effects of caffeine on performance, mood, headache, and sleep. *Neuropsychobiology*, 38, 32-41.

Jeong, D., & Dimsdale, J. E. (1990). The effects of caffeine on blood pressure in the work environment. *American Journal of Hypertension*, **3**, 749-753.

Jones, H. E., Herning, R. I., Cadet, J. L., and Griffiths, R. R. (2000). Caffeine withdrawal increases cerebral blood flow velocity and alters quantitative electroencephalography (EEG) activity. *Psychopharmacology*, **147**, 371-377.

Kirchhoff, M., Torp-Pedersen, C., Hougaard, K., Jacobsen, T. J., Sjol, A., Munch, M., Tingleff, J., Jorgensen, T., Schroll, M., & Olsen, M. E. (1994). Casual blood pressure in a general Danish population. Relation to age, sex, weight, height, diabetes, serum lipids and consumption of coffee, tobacco and alcohol. *Journal of Clinical Epidemiology*, **47**, 469-474.

Lancaster, T., Muir, J., & Silagy, C. (1994). The effects of coffee on serum lipids and blood pressure in a UK population. *Journal of the Royal Society of Medicine*, **87**, 506-507.

Lane, J. D., Adcock, R. A., Williams, R. B., & Kuhn, C. M. (1990). Caffeine effects on cardiovascular and neuroendocrine responses to acute psychosocial stress and their relationship to level of habitual caffeine consumption. *Psychosomatic Medicine*, **52**, 320-336.

Lane, J. D., & Manus, D. C. (1989). Persistent cardiovascular effects with repeated caffeine administration. *Psychosomatic Medicine*, **51**, 373-380.

Lane, J. D., and Phillips-Bute, B. G. (1998). Caffeine deprivation affects vigilance performance and mood. *Physiology and Behavior*, **65**, 171-175.

Lane, J. D., Phillips-Bute, B. G., and Pieper, C. F. (1998). Caffeine raises blood pressure at work. *Psychosomatic Medicine*, **60**, 327-330.

Lang, T., Bureau, J. F., Degoulet, P., Salah, H., & Benattar, C. (1983). Blood pressure, coffee, tea and tobacco consumption: An epidemiological study in Algiers. *European Heart Journal*, **4**, 602-607.

Lelo, A., Miners, J. O., Robson, R. A., & Birkett, D. J. (1986b). Quantitative assessment of caffeine partial clearances in man. *British Journal of Clinical Pharmacology*, **22**, 183-186.

Lewis, C. E., Caan, B., Funkhouser, E., Hilner, J. E., Bragg, C., Dyer, A., Raczynski, J. M., Savage, P. J., Armstrong, M. A., & Friedman, G. D. (1993). Inconsistent associations of caffeine-containing beverages with blood pressure and with lipoproteins. The CARDIA Study. Coronary Artery Risk Development in Young Adults. *American Journal of Epidemiology*, **138**, 502-507.

MacDonald, T. M., Sharpe, K., Fowler, G., Lyons, D., Freestone, S., Lovell, H. G., Webster, J., & Petrie, J. C. (1991). Caffeine restriction: Effect of mild hypertension. *British Medical Journal*, **303**, 1235-1238.

MacMahon, S., Peto, R., Cutler, J., Collins, R., Sorlie, P., Neaton, J., Abbott, R., Godwin, J., Dyer, A., & Stamler, J. (1990). Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*, **335**, 765-774.

Medeiros, D. M. (1982). Caffeinated beverage consumption and blood pressure in Mississippi young adults. *Nutrition Reports International*, **26**, 563-568.

Miner, M. H., McKinney, M. E., Witte, H., Buell, J. C., & Eliot, R. S. (1985). Regular caffeine consumption: Effect on resting cardiovascular function and cardiovascular changes induced by mental challenge. *Nebraska Medical Journal*, **70**, 43-48.

Myers, M. G., & Reeves, R. A. (1991). The effect of caffeine on daytime ambulatory blood pressure. *American Journal of Hypertension*, **4**, 427-431.

Myers, M. G., Shapiro, D., McClure, F., & Daimes, R. H. (1989). Caffeine and stress reactivity in Black and White males. *Health Psychology*, **8**, 248-256.

Periti, M., Salvaggio, A., Quaglia, G., & Di Marzio, L. (1987). Coffee consumption and blood pressure: An Italian study. *Clinical Science*, **72**, 443-447.

Pickering, T. G., Mann, S. J., and James, G. D. (1991). Clinic and ambulatory blood pressure measurements for the evaluation of borderline hypertension in smokers and nonsmokers. *Archives des Maladies du Coeur et des Vaisseaux*, **84** (Spec), 17-19.

Pfeifer, R. W., & Notari, R. E. (1988). Predicting caffeine plasma concentrations resulting from consumption of food or beverages: A simple method and its origin. *Drug Intelligence and Clinical Pharmacy*, **22**, 953-959.

Rachima-Maoz, C., Peleg, E., and Rosenthal, T. (1998). The effect of caffeine on ambulatory blood pressure in hypertensive patients. *American Journal of Hypertension*, **11**, 1426-1432.

Ratliff-Crain, J., O'Keefe, M. K., & Baum, A. (1989). Cardiovascular reactivity,

mood, and task performance in deprived and nondeprived coffee drinkers. *Health Psychology*, **8**, 427-447.

Rizzo, A. A., Stamps, L. E., & Fehr, L. A. (1988). Effects of caffeine withdrawal on motor performance and heart rate changes. *International Journal of Psychophysiology*, **6**, 9-14.

Robelin, M. and Rogers, P. J. (1998). Mood and psychomotor performance effects of the first, but not of subsequent cup-of-coffee equivalent doses of caffeine consumed after overnight caffeine abstinence. *Behavioural Pharmacology*, **9**, 611-618.

Robertson, D., Frölich, J. C., Carr, R. K., Watson, J. T., Hollifield, J. W., Shand, D. G., & Oates, J. A. (1978). Effects of caffeine on plasma renin activity, catecholamines and blood pressure. *New England Journal of Medicine*, **298**, 181-186.

Rodgers, A. and MacMahon, S. (1999). Blood pressure and the global burden of cardiovascular disease. *Clinical and Experimental Hypertension (New York).* **21**, 543-52.

Rogers, P. J. and Dernoncourt, C. (1998) Regular caffeine consumption: A balance of adverse and beneficial effects for mood and psychomotor performance. *Pharmacology, Biochemistry and Behavior*, **59**, 1039-1045.

Salvaggio, A., Periti, M., Miano, L., & Zambelli, C. (1990). Association between habitual coffee consumption and blood pressure levels. *Journal of Hypertension*, **8**, 585-590.

Salvaggio, J. E. (1992). Fauna, flora, fowl, and fruit: effects of the Columbian exchange on the allergic response of new and old world inhabitants. *Allergy Proceedings*, **13**, 335-344.

Shepard, J. D., al'Absi, M., Whitsett, T. L.,. Passey, R. G., and Lovallo, W. R. (2000). Additive pressor effects of caffeine and stress in male medical students at risk for hypertension. *American Journal of Hypertension*, **13**, 475-481.

Shi, D., Nikodijevic, O., Jacobson, K. A., & Daly, J. W. (1993a). Chronic caffeine alters the density of adenosine, adrenergic, cholinergic, GABA, and serotonin receptors and calcium channels in mouse brain. *Cellular and Molecular Neurobiology*, **13**, 247-261.

Shi, J., Benowitz, N. L., Denaro, C. P., & Sheiner, L. B. (1993b). Pharmacokinetic-pharmacodynamic modeling of caffeine: tolerance to pressor effects. *Clinical Pharmacology and Therapeutics*, **53**, 6-14.

Shirlow, M. J., & Mathers, C. D. (1985). A study of caffeine consumption and symptoms: Indigestion, palpitations, headache and insomnia. *International Journal of Epidemiology*, **14**, 239-248.

Silverman, K., Evans, S. M., Strain, E. C., & Griffiths, R. R. (1992). Withdrawal syndrome after the double-blind cessation of caffeine consumption. *New England Journal of Medicine*, **327**, 1109-1114.

Smits, P., Thien, T., & van't Laar, A. (1985). Circulatory effects of coffee in relation to the pharmacokinetics of caffeine. *American Journal of Cardiology*, **56**, 958-963.

Stanton, M. F., Ahrens, R. A., & Douglas, L. W. (1978). Coffee and cola beverage consumption as heart disease risk factors in man. *Experientia*, **34**, 1182-1183.

Stensvold, I., Tverdal, A., & Foss, O. P. (1989). The effect of coffee on blood lipids and blood pressure. Results from a Norwegian cross-sectional study, men and women, 40-42 years. *Journal of Clinical Epidemiology*, **42**, 877-884.

Strain, E. C., Mumford, G. K., Silverman, K., & Griffiths, R. R. (1994). Caffeine dependence syndrome. Evidence from case histories and experimental evaluations. *JAMA*, **272**, 1043-1048.

Superko, H. R., Myll, J., DiRicco, C., Williams, P. T., Bortz, W. M., & Wood, P. D. (1994). Effects of cessation of caffeinated-coffee consumption on ambulatory and resting blood pressure in men. *American Journal of Cardiology*, **73**, 780-784.

van Dusseldorp, M., Smits, P., Thien, T., & Katan, M. B. (1989). Effect of decaffeinated versus regular coffee on blood pressure. A 12-week, double-blind trial. *Hypertension*, **14**, 563-569.

Weber, J. G., Ereth, M. H., & Danielson, D. R. (1993). Perioperative ingestion of caffeine and postoperative headache. *Mayo Clinic Proceedings*, **368**, 842-845.

Yucel, A., Ozyalcin, S., Talu, G. K., Yucel, E. C., and Erdine, S. (1999). Intravenous administration of caffeine sodium benzoate for postdural puncture headache. *Regional Anesthesia & Pain Medicine*, **24**, 51-4.