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EXPERT REPORT

Genetics, metabolism and individual responses to caffeine

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Contents

Introduction and perspective

"Why is it that my wife can drink 5 cups of coffee in a day and go to sleep with ease, while I only need to drink one cup at 5pm to be wide awake in the middle of the night?"

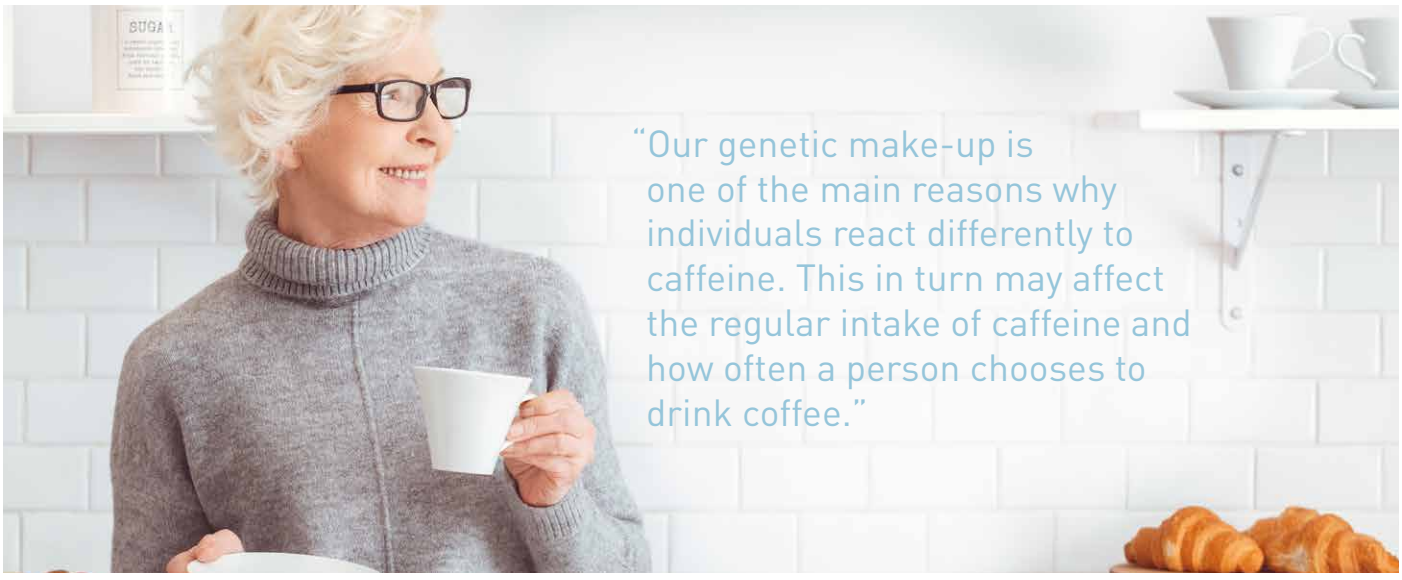
This is a question, or dilemma you might call it, that patients often ask their healthcare professional. The central question of why coffee seems to affect everyone differently is a topic of debate in homes, clinics, newspapers and research labs around the world.

The short answer to this question is that if a group of people drink the same standardised amount of coffee, say one cup with 100mg of caffeine, they will react differently. According to research, each person's unique genetic make-up determines to what degree a given amount of caffeine will affect the individual[1]. Some will metabolise caffeine quickly, while others will metabolise it more slowly. Some will show greater sensitivity to the stimulating effects of caffeine, while others need higher amounts to feel an effect[1].

Our genetic make-up is one of the main reasons why individuals react differently to caffeine. This in turn may affect the regular intake of caffeine and how often a person chooses to drink coffee. Some people, for example, drink coffee to feel more alert, and will only need one cup to feel the desired effect, whilst others may need to drink more[1,2,3].

This report gives a brief outline of the current research on genetic variability and individual responses to caffeine, and stresses the importance of taking individual responses into consideration when advising patients and consumers. We cannot give all patients, consumers, readers and viewers the same guidance regarding coffee and caffeine intake. Everyone is a unique coffee drinker.

This report is aimed at healthcare professionals, researchers and medical journalists. It is not intended as a scientific review of the literature, rather as a general overview of current scientific research, and where this research could be developed in future.

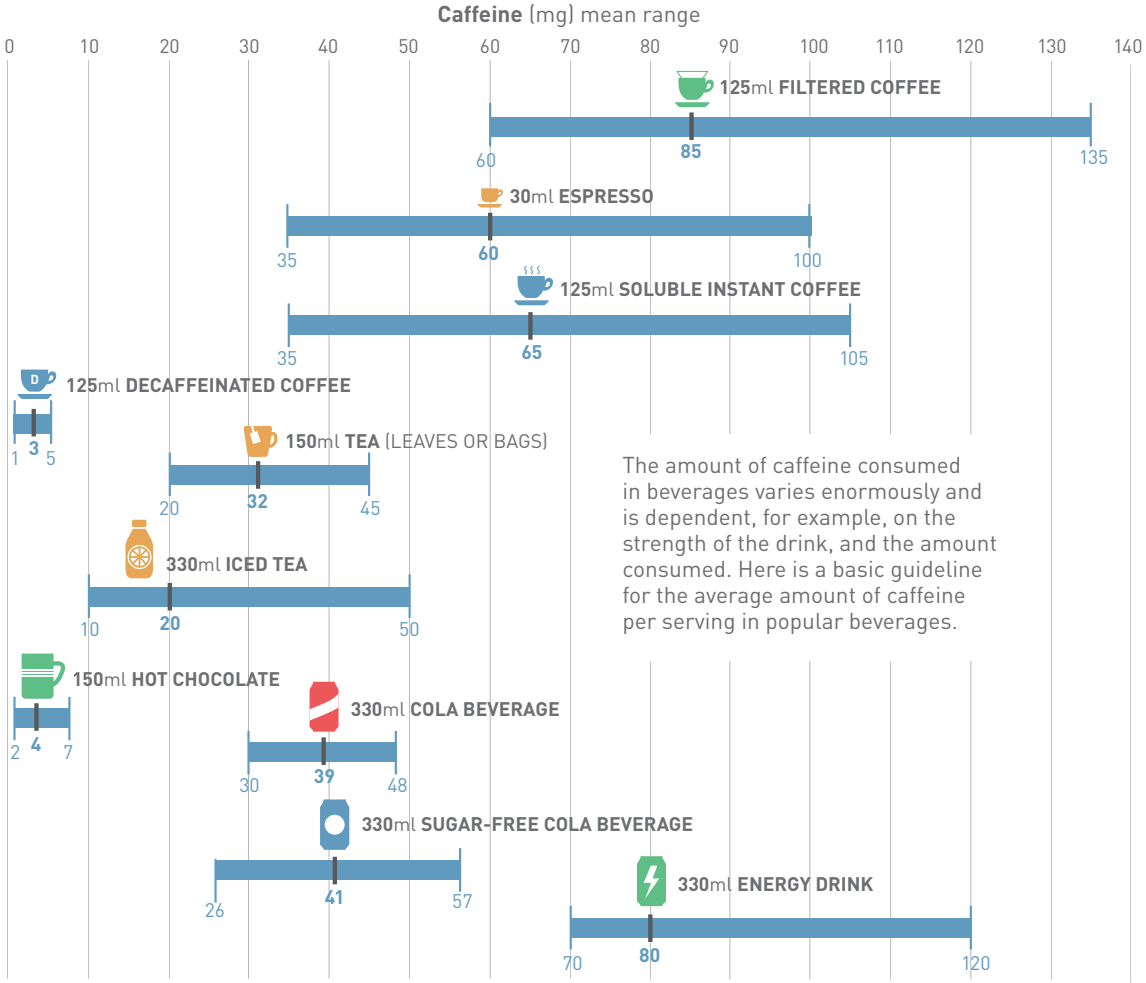


About coffee and caffeine

Coffee is one of the world's most popular and widely consumed natural stimulants in daily life, used by millions to jump-start a sluggish morning and increase alertness throughout the day.

Caffeine, a methylxanthine compound related to theophylline, is a natural substance found in a number of plant species, including coffee, tea and cocoa with varying amounts and concentrations of caffeine according to different types. A typical cup of coffee contains 75–100mg caffeine[4].

Sources of Caffeine



After ingestion, caffeine is absorbed from the stomach and intestines into the bloodstream. The stimulating effects of caffeine are associated mainly with A1 and A2A adenosine receptors, mostly in the brain. Caffeine's effects can last for several hours, depending on how quickly or slowly it is metabolised, or broken down, in the liver and excreted in the urine. Caffeine has an average half-life of approximately four hours (although this may vary) explaining why some individuals can drink coffee throughout the day and have no trouble sleeping, whilst others prefer to avoid coffee, or switch to decaffeinated coffee in the afternoon and evening[5,6].

How does the body metabolise caffeine?

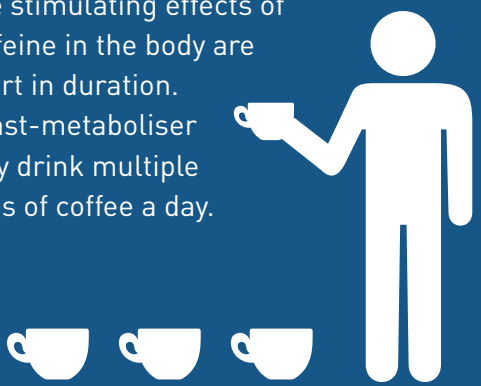
Caffeine does not accumulate in our body, but is broken down in the liver. The liver enzymes responsible for metabolising caffeine are called cytochrome P450 enzymes.

One of them is a key enzyme called CYP1A2, which is responsible for inactivating 95% of all ingested caffeine. The ability to produce this enzyme is coded for by the CYP1A2-gene. Different people have different versions of the CYP1A2-gene, and these genetic variations determine how active the CYP1A2-enzyme is in each person. This polymorphism divides people into one of two groups[1,7,8].

Someone who produces a very active version of the CYP1A2-enzyme will metabolise caffeine quickly, and it will have a shorter-lasting and mild effect throughout the body. In contrast, a person with a less active version of the CYP1A2-enzyme will inactivate caffeine more slowly and retain it in the body for longer, and therefore experience longer-lasting and more pronounced effects[8].

Based on these genetic variations, the different versions of the CYP1A2-gene split the population into the aforementioned two major groups[1,7,8]:

Fast-metabolisers
metabolise caffeine quickly. The stimulating effects of caffeine in the body are short in duration. A fast-metaboliser may drink multiple cups of coffee a day.



Slow-metabolisers
metabolise caffeine more slowly, so caffeine will be present in the body and brain for a longer period of time. The physiological effects of caffeine, such as increased alertness, will generally last longer and be more pronounced.

It should be noted, however, that genetic variability will also affect the binding of caffeine to brain receptors, which in turn will also influence how strongly an individual experiences caffeine's effects.

Genetics and the central nervous system

Caffeine's primary action is in the central nervous system. Caffeine has a similar structure to adenosine, a compound in the body that binds to adenosine receptors in the brain, leading to a chain of events that reduce stimulatory neurotransmitters such as dopamine, in turn producing the sensation of 'being tired'. Because caffeine is similar in structure to adenosine, it is able to bind to receptors in place of adenosine. When this happens, it increases feelings of alertness. This explains why a coffee drinker feels that tiredness is replaced with wakefulness, alertness, and increased concentration[5].

Adenosine receptors exist in different forms, and adenosine A2 receptors are key to the stimulating effect of caffeine. A polymorphism of the adenosine receptor (ADORA2A polymorphism) is more likely to be found in those who self-report as caffeine sensitive. People with high habitual caffeine consumption typically do not carry this ADORA2A genotype[1,6,9–12].

Major groups of caffeine sensitivity

In my view, it makes sense to propose three descriptive levels of overall caffeine sensitivity depending on both the genetic variability in liver metabolism and central nervous system sensitivity.

High sensitivity to caffeine

Slow-metabolism in the liver and high binding in the central nervous system. Even small amounts of caffeine will cause a stimulating effect and higher doses may cause sleep problems, as seen in a minority of people.

Regular sensitivity to caffeine

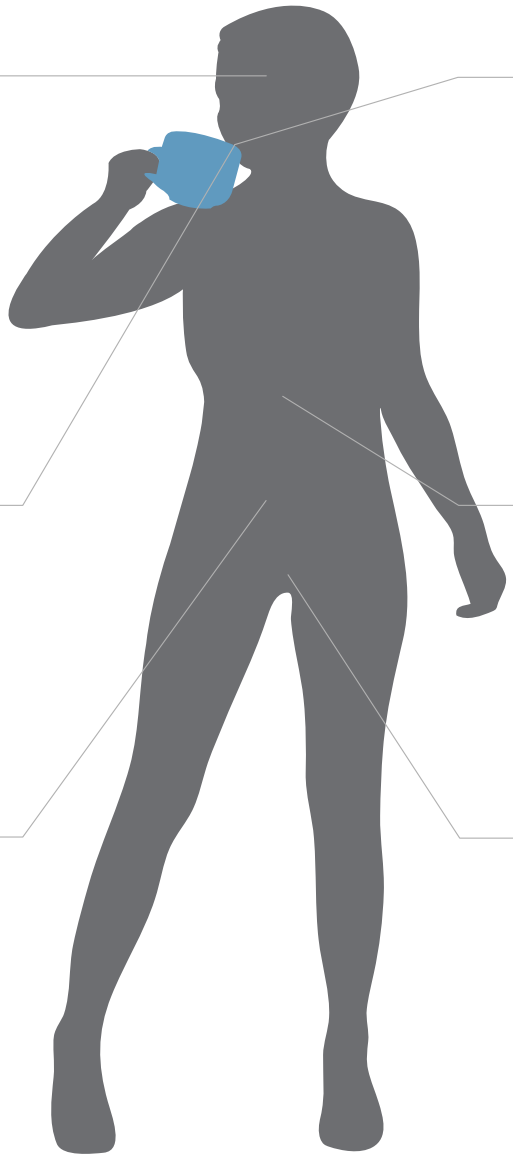
The balance between caffeine inactivation in the liver and binding in the central nervous system means that the individual can typically drink 2–5 cups of coffee during the day but without adverse reactions or sleep disturbances. Caffeine is normally not recommended in the evening, but individual differences prevail, as seen in most people.

Low sensitivity to caffeine

Fast-metabolisers of caffeine. Higher intakes can be consumed, (although healthcare professionals should advise that they still stay within the EFSA guidelines of no more than 5 cups of coffee per day[13]). Coffee drinking before bedtime does not typically disturb sleep.

Of course, this varies across a spectrum and individuals often manage their own caffeine intake to suit their personal lifestyle. It is likely that people who are more sensitive to caffeine will self-moderate their intake based on what they know they can tolerate.

Other factors affecting caffeine metabolism



Genetic variations may affect the way an individual metabolises caffeine. The population could be divided into 'slow' and 'fast' caffeine metabolisers by a specific enzyme[1,2,3].

Research suggests that **smoking** stimulates caffeine clearance and almost doubles the rate of caffeine metabolism[9,10,11].

Alcohol intake can prolong caffeine half-life and decrease caffeine clearance[4].

Certain **liver diseases** may reduce plasma clearance of caffeine[12].

Several **dietary factors** may affect caffeine metabolism[5–8]. Eating broccoli and brassica vegetables, or large quantities of vitamin C, can increase caffeine clearance[8].

The use of **oral contraceptives** doubles caffeine half-life, mainly during the second half of the menstrual cycle[13].

Other factors besides genetic make-up can affect caffeine metabolism: these include age, gender, tolerance to habitual coffee intake, smoking status, some specific medications, and pregnancy.[1,5,14].

Age does not appear to affect caffeine clearance, however responses to caffeine tend to be more marked in younger individuals.

Men and women typically show similar reactions to caffeine intake. However, in Parkinson's disease, the potential preventive effects are more marked in men than in women, though the impact of hormonal changes associated with the menopause may confound the results[15].

Tolerance to some subjective effects of caffeine, such as anxiety and jitteriness, have been reported. There is only limited evidence for tolerance to caffeine-induced alertness and wakefulness.

Smokers typically break down caffeine more quickly than non-smokers.

Drugs metabolised by the liver may impact caffeine clearance and half-life by affecting CYP1A2-enzymes in the liver. Oral contraceptives, antibiotics, calcium antagonist, beta-blockers, anticoagulants, antidepressants, antipsychotics, anti-inflammatory drugs, proton pump inhibitors and bronchodilators, among others, have potential interactions with caffeine, most often prolonging the half-life and actions of caffeine.

Pregnancy tends to slow down the rate at which caffeine is broken down, particularly during the later stages. Pregnant women are advised to limit caffeine intake to 200mg daily from all sources[13].

Practical advice

Generally speaking, most individuals tend to consume only the amount of caffeine that they feel comfortable with. This can be considered a sort of self-regulating mechanism rooted in the individual's genetic make-up and driven by their own experiences and reactions to caffeine. If an individual knows from experience that they have trouble falling a sleep after drinking coffee late at night, for example, they should simply stop late-night coffee consumption.

For this reason it is likely that those who are more sensitive to caffeine will limit their intake compared to those who are less sensitive. This behaviour helps to prevent overuse and potential unwanted effects[9].

Because individuals respond differently to caffeine depending on a number of factors, individual advice regarding coffee and caffeine intake is the most appropriate cause of action. Those with particular queries should seek medical advice.

When healthcare professionals are confronted with a patient asking for advice, it is important that they clarify how the person tolerates caffeine in daily life, and whether this has changed at all. Recent changes in the reaction pattern could indicate a disease, new medication, or other factors known to affect caffeine metabolism.

"Because individuals respond differently to caffeine depending on a number of factors, individual advice regarding coffee and caffeine intake is the most appropriate cause of action."

The general advice is the following:

- A person who is, or has recently become highly sensitive to caffeine, is recommended to consume it only in small amounts.
- For someone with regular sensitivity, a daily consumption of coffee within the recommended guidelines is safe and without problems. This individual typically drinks 2–5 cups of coffee daily[13]. The healthcare professional should point out that moderate caffeine consumption, of around 400mg caffeine or equivalent of up to 5 cups of coffee per day, for most people can be enjoyed as part of a healthy balanced diet and active lifestyle[13].
- Always remember that lower intakes are recommended for pregnant women, who are advised to limit caffeine intake to 200mg from all sources[13].
- An individual with low sensitivity to caffeine probably will not experience the typically desired effects such as wakefulness, alertness, and increased concentration. However they can, of course, still experience the taste of coffee as much as the next person. It is important for healthcare professionals to stress that fast metabolisers should not exceed the recommended daily caffeine intake trying to achieve the desired effects.

Areas for further research

The research into the importance of genetics in habitual caffeine intake and its physiological effects is still in its infancy. There is a lot more to be learned.

Further research into caffeine could categorise populations further by gene types and investigate what this could mean for various physiological functions during caffeine consumption.

A better understanding of the factors influencing intake, metabolism and brain receptor binding of caffeine could be an opportunity to gain further knowledge and new information about the prevention and treatment of a number of chronic diseases, as coffee and caffeine consumption have been linked to a reduced risk of a number of diseases, such as type 2 diabetes, cardiovascular disease, and neurodegenerative disorders such as Parkinson's Disease. More recent research also suggests that coffee could be linked reduced overall mortality.

About Dr J.W. Langer

Dr Langer is a physician, author, and media commentator. He is a clinical pharmacology lecturer at Copenhagen University's Medical School and the author of several books on nutrition, blood pressure, exercise, healthy lifestyle, and self-care. He has over 25 years' experience in translating hard science into everyday language and is frequently invited to provide his expert commentary on television, radio and in newspapers, discussing issues such as nutrition, exercise, health and wellness.

About ISIC

The Institute for Scientific Information on Coffee (ISIC) is a not-for-profit organization, established in 1990 and devoted to the study and disclosure of science related to "coffee and health." Since 2003 ISIC also supports a pan-European education programme, working in partnership with national coffee associations in nine countries to convey current scientific knowledge on "coffee and health" to health care professionals.

ISIC's activities are focused on:

- the study of scientific matters related to "coffee and health"
- the collection and evaluation of studies and scientific information about "coffee and health"
- the support of independent scientific research on "coffee and health"
- active dissemination of balanced "coffee and health" scientific research and knowledge to a broad range of stakeholders.

ISIC respects scientific research ethics in all its activities. ISIC's communications are based on sound science and rely on scientific studies derived from peer-reviewed scientific journals and other publications.

ISIC members are six of the major European coffee companies: illycaffè, Jacobs Douwe Egberts, Lavazza,Nestlé, Paulig, and Tchibo.

About coffeeandhealth.org

The website www.coffeeandhealth.org is a science-based resource developed for health care and other professional audiences and provides the latest information and research into coffee, caffeine and health.

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References

1 Nehlig A. (2018) Inter-individual differences in caffeine metabolism and factors driving caffeine consumption *Pharmacol Rev.* 70(2):384–41.

2 Brunyé T.T. et al. (2010) Acute caffeine consumption enhances the executive control of visual attention in habitual consumers. *Brain Cogn,* 74:186–92.

3 EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (2011) Scientific Opinion on the substantiation of health claims related to caffeine and increased fat oxidation leading to a reduction in body fat mass (ID 735, 1484), increased energy expenditure leading to a reduction in body weight (ID 1487), increased alertness (ID 736, 1101, 1187, 1485, 1491, 2063, 2103) and increased attention (ID 736, 1485, 1491, 2375) pursuant to Article 13(1) of Regulation (EC) No 1924/20061. *EFSA Journal,* 9(4):2054.

4 Heckman M.A. et al. (2010) Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. *J Food Sci,* 75:R77–87.

5 Fredholm B.B. et al. (1999) Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev,* 51:83–133.

6 Yang A. et al. (2010) Genetics of caffeine consumption and responses to caffeine. *Psychopharmacol,* 211(3):245–257.

7 Sachse C. et al. (1999) Functional significance of a C–→A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. *Br J Clin Pharmacol,* 47(4):445–9.

8 Denden S. et al (2016) Gender and ethnicity modify the association between the CYP1A2 rs 762551 polymorphism and habitual coffee intake: evidence from a meta-analysis. *Genet Mol Res,* 15(2).

9 Retey J.V. et al. (2007) A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clin Pharmacol Ther,* 81:692–8.

10 Childs E. et al. (2008) Association between ADORA2A and DRD2 Polymorphisms and Caffeine-Induced Anxiety, *Neuropsychopharmacol,* 33(12): 2791–2800.

11 Rogers P.J. et al. (2010) Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. *Neuropsychopharmacol,* 35(9): 1973–83.

12 Cornelis M. et al. (2007) Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. *Am J Clin Nutr,* 86: 240–244.

13 EFSA (2015) Scientific Opinion on the Safety of Caffeine, *EFSA Journal,* 13(5):4102

14 Arnaud M.J. (2011) Pharmacokinetics and metabolism of natural methylxanthines in animal and man. *Handb Exp Pharmacol,* (200):33–91.

15 Ascherio A. et al. (2003) Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. *Neurology,* 60:790–5.

References for infographic

1 Nehlig A. (2017) Interindividual differences in caffeine metabolism and factors driving caffeine consumption. *Pharmacol Rev,* 70(2)384–411.

2 Yang A. et al. (2010) Genetics of caffeine consumption and responses to caffeine. *Psychopharmacol,* 211(3):245–257.

3 Arnaud M.J. (2011) Pharmacokinetics and metabolism of natural methylxanthines in animal and man. *Handb Exp Pharmacol,* (200):33–91.

4 George J. et al. (1986) Influence of alcohol and caffeine consumption on caffeine elimination. *Clin Exp Pharmacol Physiol,* 13:731–736.

5 Fuhr U. et al. (1993) Inhibitory effect of grapefruit juice and its bitter principal, naringenin, on CYP1A2 dependent metabolism of caffeine in man. *Br J Clin Pharmacol,* 35:431–436.

6 Fuhr U. et al. (1995) Lacking effect of grapefruit juice on theophylline pharmacokinetics. *Int J Clin Pharmacol Ther,* 33:311-314.

7 Blanchard J. & Hochman D. (1984) Effects of vitamin C on caffeine pharmacokinetics in young and aged guinea pigs. *Drug Nutrient Interactions,* 2:243–255.

8 Lampe J.W. et al. (2000) Brassica vegetables increase and apiaceous vegetables decrease cytochrome P450 1A2 activity in humans: changes in caffeine metabolite ratios in response to controlled vegetable diets. *Carcinogenesis*, 21:1157–1162.

9 Kalow W. & Tang B.K. (1991) Caffeine as a metabolic probe: exploration of the enzyme-inducing effect of cigarette smoking. *Clin Pharmacol Ther*, 49:44–48.

10 Parsons W.D. & Neims A.H. (1978) Effect of smoking on caffeine clearance. *Clin Pharmacol Ther*, 24:40-45.

11 Brown C.R. et al. (1988) Changes in rate and pattern of caffeine metabolism after cigarette abstinence. *Clin Pharmacol Ther*, 43(5) 488–91.

12 Scott N.R. et al. (1988) Caffeine clearance and biotransformation in patients with chronic liver disease. *Clin Sci*, 74: 377-384.

13 Arnaud M.J. (1993) *Metabolism of caffeine and other components of coffee, in Caffeine, Coffee and Health (Garattini S ed)*, pp 43–95.