COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON THE REPRODUCTIVE EFFECTS OF CAFFEINE

Background

1. Caffeine is present in coffee, tea, chocolate, cocoa, cola drinks, many of the increasingly popular 'energy drinks', and in over-the-counter and prescription medications including many cold and 'flu remedies, headache treatments, diet pills, diuretics and stimulants. Most pregnant women in the UK consume caffeine from one or more sources.

2001 COT Evaluation

2. The Committee last considered possible adverse effects of caffeine consumption on reproduction in 2001 and issued a statement at that time with the following conclusions. [1]

3. "We note that the risk of low birth weight and spontaneous abortion increases with increasing maternal caffeine intake during pregnancy. However, a threshold level of caffeine intake, above which maternal caffeine intake presents a risk to pregnancy, cannot be determined. Different studies assume different caffeine contents of beverages and this leads to some variation in the levels of caffeine intake associated with adverse effects on reproduction in different studies. We consider it prudent to assume that caffeine intakes above 300 mg/day show a plausible association with low birth weight and spontaneous abortion, given the available evidence from studies in experimental animals and epidemiological studies. However, on the basis of the available evidence, it is not possible to define this association as causal. We note that 300 mg/day caffeine is equivalent to four cups of instant coffee or about six cups of tea, assuming average caffeine contents.

4. We note that for caffeine intakes of 150 to 300 mg/day there is less evidence for an association, with greater inconsistency in the results of epidemiological studies than for intakes above 300 mg/day.

5. We note that data on maternal caffeine consumption during pregnancy and associations with adverse effects on reproduction other than low birth weight and spontaneous abortion, such as pre-term birth and adverse effects on the fetus are inconclusive. We do not consider there to be reliable evidence for associations with these parameters at moderate consumption levels (below 300 mg/day).

6. There do not appear to be effects of caffeine consumption on male fertility. Evidence for adverse effects on female fertility is inconclusive.

7. We note that the studies used to establish this association focused on caffeine intake from coffee, and that a possible influence of other constituents of coffee cannot be excluded. We also recognise that coffee and tea are just two sources of caffeine and do not necessarily represent the main sources of caffeine intake for all people.

8. Further studies are required to establish whether the observed association is causal. These might include the use of biomarkers of caffeine intake."

The FSA funded research projects (T01032 & T01033)

9. In light of the Committee's conclusions in 2001, the Food Standards Agency issued advice that caffeine intake during pregnancy should be limited to not more than 300 mg/day and offered guidance on amounts of caffeine in different foods and drinks. In addition, the Agency commissioned a prospective study, involving around 2500 pregnant women, in order to reduce uncertainties in the risk assessment and provide a more robust basis for the Agency's advice to pregnant women on caffeine consumption.

10. This research was funded as two linked projects, 'Determination of maternal caffeine intakes associated with increased risk to the fetus' (FSA project code T01032, University of Leicester) and 'Assessment of caffeine consumption, altered caffeine metabolism and pregnancy outcome' (T01033, University of Leeds).

11. The FSA-funded research was designed to overcome some of the limitations of earlier studies. It was prospective in design, recruiting women at approximately 12 weeks of gestation, and ascertained caffeine consumption and other relevant exposures through a structured questionnaire. The questionnaire, which was completed on three occasions (once in each trimester of pregnancy), detailed all sources of caffeine, as well as gathering information about other aspects of diet (including alcohol consumption), smoking habits, drug use (medicinal and recreational), work, physical activity and symptoms. The information was recorded for each 4 week period of pregnancy. The main outcome measure was fetal growth restriction (FGR) defined as failure of the baby to attain its growth potential as determined by genetic and environmental factors. A weakness of many of the previous epidemiological studies had been their reliance on birth weight as the endpoint for assessing fetal growth. It is well recognised that low birth weight does not necessarily indicate poor growth, and depends also on gestational age at birth and on other factors such as maternal height, ethnicity and parity. Given that approximately 10% of babies were expected to have FGR, each of the two study sites recruited in the region of 1,250 women in order to ensure sufficient statistical power to detect small differences in the prevalence of FGR births according to caffeine intake.

12. FGR is an important outcome because it is associated with an increased risk of perinatal mortality and morbidity, including perinatal asphyxia. Moreover, there is

epidemiological evidence that FGR correlates with adverse effects in adult life[2,3]. For example, affected individuals have an increased incidence of metabolic syndrome, manifesting as obesity, hypertension, hypercholesterolemia, cardiovascular disease, and type 2 diabetes[4,5,6].

13. Of the four primary routes of caffeine metabolism in humans, 3-demethylation is quantitatively the most important, the caffeine being converted to paraxanthine by CYP1A2. Studies have shown there to be varying levels of CYP1A2 activity in humans. Women recruited to the study were asked to participate in a "caffeine challenge" at approximately 14 and 28 weeks of gestation in order to assess metabolic phenotype for caffeine metabolism. Participants drank a defined volume of caffeine-containing cola and provided saliva samples, which allowed the half-life of caffeine and the ratio of its metabolites to be measured. Cotinine was also measured in these samples to verify reported smoking habits.

14. The Committee was presented with a pre-publication draft of the primary manuscript from these studies. The subjects' mean caffeine consumption was reported to decrease from 238 mg/day to 139 mg/day during the first trimester of pregnancy, and then increased to 153 mg/day by the third trimester. The major contributions to caffeine consumption in pregnancy were from tea (62%), coffee (14%) and cola drinks (12%), whilst chocolate contributed 8%. After adjustment for various potential confounders, caffeine consumption was associated with an increased risk of FGR which was statistically significant at intakes of 200-299 mg/day and above (Table 1).

Table 1
Odds ratios for FGR from a logistic regression analysis that adjusted for smoking status, amount smoked (cotinine concentration), and alcohol intake.

	Caffeine (mg/day)	OR	(95% CI)	p_{trend}
Average intake over pregnancy	<100	1	-	
	100-199	1.2	(0.9, 1.6)	
	200-299	1.5	(1.1, 2.1)	
	300+	1.4	(1.0, 2.0)	P=0.02

15. The relation between FGR and caffeine intake during pregnancy was modelled using the best-fitting second-order fractional polynomial (Figure 1). The curve in Figure 1 was derived from a model that took into account other risk factors such as salivary cotinine levels, self-reported alcohol consumption, maternal height, weight, ethnicity, parity, gestation at delivery and gender of the neonate. The results were robust to exclusion of those women with high risk pregnancies, multiparity, and extremely high or low caffeine intakes. For all levels of caffeine intake, lower intakes of caffeine were associated with lower risk of fetal growth restriction. It is possible that the steep decline in risk associated with caffeine intakes of less than 30 mg/day may be attributable to residual confounding. This analysis suggested a continuously increasing risk across the exposure range, and gave no indication of a threshold level

of exposure, below which risk was not elevated. The Committee requested a repeat of this analysis, excluding those women who consumed more than 300 mg caffeine per day. This confirmed that the high level consumers did not materially alter the shape of the exposure-response curve.

16. Further statistical analysis with regression models (logistic regression for binary outcomes, e.g. FGR vs no FGR, and linear regression for continuous outcomes, e.g. birth weight centile) gave no indication of important residual confounding by smoking.

17. Analysis of the data on half-lives of caffeine (as a proxy for metabolism) in saliva suggested an increased risk of FGR in fast metabolisers (shorter half life) as compared with slow metabolisers (longer half life), although the difference was not statistically significant (P=0.06).

18. It is interesting that among the women with caffeine intakes > 300 mg/day prior to pregnancy, a subset had chosen to reduce their caffeine intake to <50 mg/day by weeks 5-12 of pregnancy (n=109). The mean birth weight of infants in this subset was higher than that in women who maintained their caffeine intake above 300 mg/day (n=193) (difference in birth weight=161g, 95% CI: 24 to 297g, p=0.02). However, these two groups of women may have differed in other ways apart from their caffeine intakes.

19. The Committee noted that energy intake needed to be considered as a potential confounder of effects on fetal growth rate. Energy intake had been recorded in the Leeds arm of the study, but not in Leicester. An analysis of data from Leeds that adjusted for energy intake indicated that energy intake did not importantly confound the risk estimates for caffeine in this study.

Literature review (post-2001 COT statement)

20. In addition to being presented with the results from the FSA-funded research, the Committee was provided with an update on relevant research on reproductive effects of caffeine in humans published since the previous COT review. Table 2 summarises the key data provided to the Committee in tabular form. The references detailed in Table 2 were sourced through a systematic search of key scientific databases, details of which are given in Annex A.

21. It was noted that published studies differed substantially in their design, which may account for some of the variation in the estimated risks of adverse reproductive outcomes reported for specified levels of caffeine intake.

22. Most studies assessed caffeine intake at various stages of pregnancy, generally by use of dietary questionnaires. In most reports, caffeine intakes were assessed by multiplying the number of servings of a beverage or food by an estimated mean caffeine content, and different studies assumed different caffeine contents for beverages and foods. Further variation may have been introduced according to whether participants were asked to estimate serving size or the researcher assumed a default serving size.

23. Errors in recall would be expected to affect the accuracy of information provided on caffeine intake and on potential confounders, particularly in studies where information was gathered retrospectively. In case-control studies that ascertained caffeine intake after the outcome of pregnancy was known, differential errors may have spuriously exaggerated risk estimates. It should also be noted that many of the studies did not assess caffeine intake from all sources.

24. There is considerable inter-individual variation in caffeine metabolism, and measures of caffeine consumption do not necessarily indicate the levels of caffeine and caffeine metabolites in the maternal or fetal circulation. A small number of studies therefore measured levels of caffeine and its metabolites in maternal or umbilical cord blood rather than assessing caffeine consumption.

25. Further variation in estimates of caffeine effect may have occurred because the range of confounding factors that was taken into account differed between studies. Notably, several studies did not adjust for smoking or nausea during pregnancy.

26. Caffeine consumption greater than or equal to 300 mg/day was reported in several studies[7-14] to be associated with FGR, decreased mean birth weight, miscarriage, or increased risk of still birth, with one study finding a doubled risk of miscarriage for caffeine intakes above 200 mg/day[15]. Another study in pregnant women with Type 1 diabetes suggested an increased risk of miscarriage for a caffeine intake of just 1-2 caffeine-containing beverages per day in the first trimester, compared to non-consumers, although the elevation of risk only reached statistical significance for daily intakes of three or more drinks[16]. On the other hand, there were well-conducted studies that reported no statistically significant association between maternal caffeine intake and miscarriage, FGR, still birth or prematurity, after adjustment for potential confounders[17-21]. Overall, the findings were consistent with an increased risk of FGR and miscarriage from higher consumption of caffeine, but because of limitations in study designs (e.g. inaccurate assessment of caffeine exposures, potential for recall bias in case-control studies, and possible residual confounding), they do not allow firm conclusions about the relation of risk to levels of exposure.

27. Fewer studies looked at CYP1A2 activity and pregnancy outcomes, due to substantial confounding by smoking status, which is hard to correct for. One investigation suggested an increased risk of FGR in women with fast metabolic phenotype[22], while another found an association of caffeine intake with miscarriage only in women with low CYP1A2 activity[23].

Related observations from studies using experimental animals

28. The potential reproductive effects of caffeine have been studied in a wide range of species and strains of animals. In studies administering repeat doses of caffeine (12.5 mg/kg body weight per day and higher) to rats throughout pregnancy, significantly decreased birth weights have been noted[24]. It is not possible to determine whether this was due to a direct effect of caffeine on the fetus or secondary to decreased maternal body weight gain since it was observed only when there was a decrease in maternal body weight gain. In mice administered caffeine in

drinking water at levels equating to consumption of 22, 44 and 88 mg/kg/day a reduction in number of live pups/litter of 15 and 20% was observed in the medium and high dose level group, respectively. For the F_0 animals there were no effects on body weight, but alopecia occurred in 55% of the medium dose and 50% of the high dose animals[25].

29. Studies in the Cynomolgus monkey, *Macaca fascicularis*, have shown a high rate of still births and miscarriage with maternal caffeine intakes of 10-15 mg/kg body weight per day, given via drinking water[26]. In 2001 the COT noted "*that the main serum metabolite of caffeine in monkeys is theophylline, whereas in humans it is paraxanthine and that information on the comparative toxicities of these metabolites is not available*." It should be noted that the Cynomolgus monkey does not constitutively express CYP1A2 (which is the main enzyme responsible for caffeine metabolism) [27].. Thus, for a given dose of caffeine, the monkeys' systemic exposure is likely to be higher. Furthermore, there were limitations in the study design and therefore this study is not informative for assessing the risks of caffeine intake in humans.

Committee discussion

30. With regard to the new FSA-funded research, FGR was considered to be a relatively robust endpoint, unlike miscarriage, which is difficult to ascertain reliably as it often occurs before women know they are pregnant, or before they have been recruited to a study. Members noted that decreases in birth weight of as little as 10-15 g can have implications for future health outcomes, particularly in pre-term babies.

31. Caffeine consumption was assessed retrospectively by means of a questionnaire completed at interview at the end of each of the three trimesters of pregnancy, women being asked to recall their caffeine consumption during 4 week periods. Data on caffeine intake from all sources were recorded (tea, coffee, hot chocolate, soft drinks, chocolate) including information on brand, serving size and preparation of product. Caffeine consumption is likely to have been estimated with reasonable accuracy as, because of the repeated administration of the questionnaire, recall was recent and for most before pregnancy outcome or birth weight were known. Salivary cotinine measurement confirmed the accuracy with which the women reported their smoking habits.

32. The half-life of caffeine was measured in women in a "caffeine challenge" the *a priori* hypothesis being that an increased half-life would be associated with an increased risk of FGR, based upon the assumption that clearance would remove the potential hazard. However, this was not found. Rather, the analysis suggested that if anything, risk of FGR was higher in faster metabolisers than in slower metabolisers. This result is consistent with the findings of Grosso et al[22], who reported increased risk of intrauterine growth retardation (IUGR) in association with serum paraxanthine levels >149 ng/ml and higher paraxanthine/caffeine ratios. There are no reports of animal studies investigating reproductive effects of paraxanthine.

33. It was noted that adjustment for various potential confounding factors had little impact on risk estimates.

34. The fact that repeat modelling of the risk of FGR according to caffeine intake showed a similar dose-response relation after exclusion of women with caffeine intakes in excess of 300 mg per day suggested that the modelled relationship was not unduly influenced by findings for women with the highest caffeine intakes. The Committee noted the possibility that fitting a different mathematical model to the data may have importantly influenced the dose-response relationship observed in Figure 1, and that there was considerable uncertainty about the shape of the dose-response relationship at lower intakes. They noted that the model used placed weight on those with intakes below 50 mg/day (who may have differed in their exposure to confounding lifestyle factors) and questioned whether it was the most appropriate choice. Hence it would be inappropriate to attempt to determine a threshold dose from this figure.

Committee conclusions

35. We consider that the FSA-funded research contributes usefully to the body of evidence on the relation between caffeine intake and adverse birth outcomes.

36. From this work and from the other studies that have been published, we conclude that caffeine intake during pregnancy is associated with an increased risk of FGR. It is still not possible to be confident that the association is causal rather than a consequence of residual confounding, but it would be prudent to assume causation.

37. The evidence that is now available does not make it possible to identify a threshold level of caffeine intake below which there is no elevation of risk, and it seems likely that risk is increased in association with intakes in the order of 200 mg per day and perhaps even lower. However, if the relation is indeed causal, then the absolute increase in incidence of FGR from intakes less than 200 mg per day is likely to be less than 2% of infants.

38. The literature suggests a positive association of caffeine intake with miscarriage, but there are uncertainties relating to possible recall bias and residual confounding.

39. Data on maternal caffeine consumption during pregnancy and associations with adverse effects other than FGR and spontaneous miscarriage, such as pre-term birth and congenital malformations, are inconclusive.

Figure 1 Modelled relation between risk of fetal growth restriction (FGR) and caffeine intake (mg/day) during pregnancy.

The relation is modelled by the best-fitting second-order fractional polynomial, with 95% confidence intervals. For clarity, the graph is restricted to caffeine intakes <500mg/day. Horizontal dotted lines mark national average risk of FGR (10%) and the average risk in the cohort (13%).

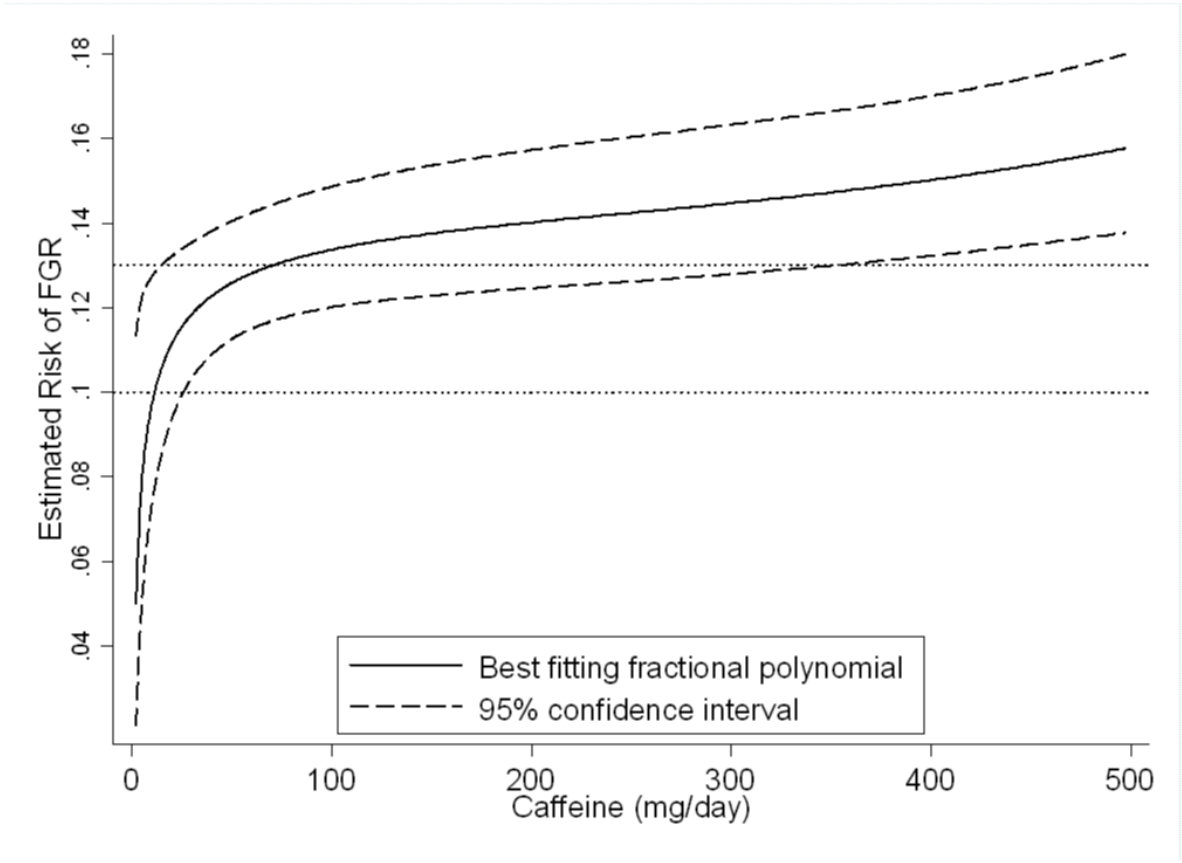

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Table 2. Key data from relevant human studies published since the previous COT review

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Studies on Birth Weight							
Balat et al (2003)[7] Turkey	Not stated	BW, length and head circumfer-ence, weight and diameter of placenta	63 pregnant non-smokers + 60 pregnant smokers with spontaneous vaginal deliveries in gestational wks 37-41	Daily consumption of tea and coffee (#cups) Participants grouped as daily caffeine intake < or > 300 mg/day	Non-smokers and smokers consuming >300 mg/day had significantly lower newborn and placental weights than those consuming <300 mg/day. No differences in other parameters.	Not reported	No adjustment reported.
Bech et al (2007)[26] Denmark	1998-2002	Birth weight and length of gestation	1207 pregnant women drinking at least 3 cups of coffee/day, recruited before 20 wks gestation	Randomised to drink caffeinated (n=568) or decaffeinated (n=629) instant coffee at usual consumption levels Interviewed throughout pregnancy on daily consumption coffee, tea, cola and cocoa	No significant differences in mean bw or mean length of gestation between caffeinated and decaffeinated groups. Mean bw of babies of women in the decaffeinated group was 16 g (95% CI: -40, +73) higher than those from the caffeinated group.	Not reported	Adjustment for length of gestation, parity, prepregnancy BMI and smoking at entry to study. Women were not asked to avoid intake of other caffeinated beverages.

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Bicalho and Barros Filho (2002)[27] Brazil	1994-1995	LBW, prematurity and IUGR	354 newborns with bw <2,500 g (cases) 354 newborns ≥3,000 g (controls)	Daily consumption of coffee, tea and soft drinks	No association between caffeine consumption during pregnancy and low birthweight, prematurity and intrauterine growth restriction.	Caffeine (mg/day) LBW <300 0.72(0.45,1.25) ≥300 0.47(0.24,0.92) IUGR <300 1.16(0.45,3.01) ≥300 0.64(0.20,1.98)	Abstract only in English. Adjustment for age, schooling, income, marital status, skin colour, parity, smoking, previous lbw child, pre-pregnancy weight, employment status, interval between pregnancies, prenatal care and high blood pressure
Bracken et al (2003)[29] USA	1996-2000	IUGR LBW	2,291 women with singleton live births	Interviews on coffee, tea and soda consumption - Interview on trimester 1 intake conducted before gestation wk 25 - Post natal interview on trimester 3 intake Urine analysis at interview 1	No significant association of caffeine consumption in trimesters 1 or 3 or urinary caffeine with the various endpoints. Mean bw reduced by 28 g per 100 mg caffeine consumed daily in trimester 1 [vs 178g reduction for smoking 10 cigarettes daily in trimester 3].	Trimester 1 Caffeine (mg/Day) IUGR 1-149 1.35(0.95,1.92) 150-299 1.05(0.53,2.09) ≥300 1.75(0.81,3.76) LBW 1-149 1.45(0.89,2.35) 150-299 1.59(0.70,3.60) ≥300 1.32(0.46,3.78) Reference: average 0 mg/day	Adjustment for age, parity, # prior pregnancies, marital status, race, education, height, smoking in 3rd trimester, weight. Similar ORs reported for caffeine consumption in trimester 3.

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)		Comments
Clausson et al (2002)[32] Sweden	1996-1998	BW, gestational age, BW standardised for gestational age (BW ratio)	873 women with singleton live births	Interviews in gestational wks 6-12 and 32-34 on intake of coffee, tea, soft drinks, cocoa, chocolate and caffeine containing medication	No associations between caffeine consumption and the endpoints assessed, neither when caffeine exposure averaged from conception to gestational wks 32-34, nor when stratified by trimester	Not reported		Adjustment for age, height, BMI, country of birth, parity, previous LBW infant, education, work, nausea, vomiting, fatigue diabetes and hypertensive disorders
Grosso et al (2006)[22] USA	1996-2000	IUGR	Pregnant women at ≤24 gestational wks: 718 consuming ≥150 mg/day caffeine in previous wk 2,915 consuming < 150 mg/day in previous wk	Caffeine and primary metabolites measured in umbilical cord blood	Higher serum caffeine levels associated with reduced risk IUGR. Paraxanthine levels ≥149 ng/ml associated with increased risk. Increase in paraxanthine:caffeine ratio increased likelihood of IUGR.	Standard deviation increase in paraxanthine:caffeine ratio No statement of baseline	1.21(1.07,1.37)	Adjustment for smoking in trimester 3, parity, pre-pregnancy wt, maternal race and maternal age at delivery
Infante-Rivard, (2007)[17] Canada	1998-2000	SGA	493 SGA cases, 480 controls	Interview within 2 days of delivery on number of cups of coffee, tea and cans of cola daily for each trimester, and month before pregnancy	No association caffeine consumption and SGA overall (smokers and non-smokers combined). ORs for caffeine intake in trimester 1 statistically heterogeneous between smokers and non, authors suggest an increased risk for non-smokers	Caffeine (mg/day) ≥300 in trimester 1 vs <300 Reference category: <300 mg/day	Smokers 0.43(0.18,1.03) Non smokers 2.13(0.82,1.03) Heterogeneity: p=0.01	Adjustment for, nausea, race, pre-pregnancy BMI, parity. Smoking also adjusted for when analysis not stratifying smokers and non-smokers

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Klebanoff et al (2002)[34] USA	1959-1966	SGA	2,515 women	Paraxanthine levels in serum collected in trimester 3 (>26 wks of gestation)	Mean levels higher in women with SGA babies (754 ng/ml) vs women with NGA babies (653 ng/ml) Significant linear trend for smokers but not non-smokers before adjustment	Not reported	Adjustment for maternal age, pre-pregnancy weight, education, parity, ethnicity and no. cigarettes smoked per day
Ørskou et al (2003)[36] Denmark	1990-1999	High birth weight (>4,000 g)	24,093 non-diabetic pregnant women	Questionnaire at approx. 16 wks gestation on average daily coffee intake	Women with a caffeine intake of >200 mg/day had a statistically reduced 'risk' of giving birth to an infant weighing > 4,000 g compared to women with an intake of <200 mg/day.	OR for high BW Caffeine (mg/day) 300-399 0.88(0.81,0.96) ≥400 0.87(0.79,0.95) Reference: <200 mg/day	Adjustment for pre-pregnancy weight and height, parity, smoking, alcohol, marital status, education level, gestational age and infant gender
Parazzini et al (2005)[19] Italy	Not stated	SGA	555 women with SGA babies [<10th percentile based on Italian standard] (cases) 1966 women with term babies of normal weight (controls)	Interviews on tea, cola and coffee intake prior to pregnancy and in each trimester	No significant associations between tea, cola, caffeinated coffee or decaffeinated coffee consumption and SGA	Coffee (≥3 cups/day) Trimester 1 1.2(0.8,1.8) Trimester 2 1.2(0.8-1.8) Reference category: 0 cups/day Trimester 3 0.9(0.6,1.4)	Adjustment for age, education, parity, smoking in trimester 3, gestational hypertension and history of SGA birth

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Vik et al (2003)[14] Sweden	1986-1988	SGA	111 mothers of small for gestational age (SGA) babies 747 mothers of non-SGA babies	3-day food records collected in Trimesters 2 and 3. Caffeine intake calculated from tea, coffee, soft drinks and chocolate, classed as high or low based on median	Mean caffeine intake higher in SGA mothers than controls in trimester 3 (281 vs 212 mg/day) but not in trimester 1	Caffeine intake classed as high/low based on median High intake week 17 1.1(0.6,2.1) High intake week 33 1.6(1.0,2.5) High avge intake over pregnancy 1.5(1.0,2.4) No statement of baseline	Adjustment for smoking at conception, pre-pregnancy wt, low education, previous SGA birth High mean caffeine intake in trimester 3 or in trimester 1 and 3 combined associated with increased risk for SGA birth of male but not female babies
Xue et al (2007)[43] USA	Inform-ation collected from mothers in 2001-2002	BW, IUGR	34,063 women in Nurse's Mother Cohort	Interviews conducted on coffee intake when pregnant with their nurse daughters	Daily consumption of each additional cup of coffee associated with a 10g decrease in bw	Coffee (cups/day) IUGR <1 1.00(0.82,1.21) 1-2 1.28(1.12,1.47) 3-4 1.30(1.10,1.55) >5 1.63(1.25,2.12) Trend test (cup/day) 1.09(1.05,1.13) Baseline: Never drank coffee	Interviews with mothers conducted a long time after pregnancy - when their offspring were adults Adjustment for maternal BW, height, BMI, birth order, maternal weight gain, diabetes in pregnancy, smoking, gestational age, occupation, maternal milk consumption, paternal BMI, maternal infertility

Studies on miscarriage, stillbirth and infant death							
Author + location	**Study period**	**Outcome variables**	**Study sample**	**Measure of caffeine exposure**	**Study authors description of results**	**OR/RR (95% CI)**	**Comments**
Bech et al (2005)[8] Denmark	1996-2002	Fetal death (miscarriage or stillbirth)	88,482 pregnant women recruited into Danish National Birth Cohort by GPs	Telephone interview at approx gestational wk 16 on daily coffee consumption	High levels of coffee consumption associated with an increased risk of fetal death	Cups coffee/day: 0.5-3 1.03(0.89,1.19) 4-7 1.33(1.08,1.63) ≥8 1.59(1.19,2.13) Reference category: 0 cups coffee/day	Adjustment for age, parity, smoking, pre-pregnancy BMI, alcohol consumption, socio-occupational status
George et al (2006)[10] Sweden	1996-1998	Repeated miscarriage	108 women with ≥2 consecutive miscarriages (cases) 953 control women matched by wks of gestation	Interviews within 2-6 wks of miscarriage on intake of coffee, tea, cocoa, chocolate, soft drinks and caffeine-containing medication	Mean caffeine intake 311 mg/day in cases, 240mg/day for controls	Mean caffeine intake in pregnancy (mg/day) Smokers 100-299 0.5 (0.04,6.9) ≥300 0.4 (0.05,4.1) Non smokers 100-299 1.9 (0.8,4.3) ≥300 2.7 (1.1,6.2) Reference: 0-99 mg/day	Adjustment for age, previous pregnancy history, induced abortions, myoma, time to conceive, alcohol intake and folate levels

Giannelli et al (2003)[11] UK	1987-1989	Miscarriage	160 nulliparous women with miscarriage (cases) 314 nulliparous pregnant women attending for antenatal care in trimester 3.	Interview 3 wks after miscarriage or at antenatal appointment on coffee, tea and cola consumption	Caffeine consumption >300 mg/day during pregnancy associated with an increased risk of miscarriage	Caffeine intake in pregnancy (mg/day) 151-300 1.19(0.67,2.12) 301-500 1.94(1.04,3.63) >500 2.18(1.08,4.40) Reference: ≤ 150 mg/day	Adjustment for maternal age, severity of nausea and gestational age.

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)		Comments
Karypidis et al (2006)[12] Sweden	1996-1998	First trimester miscarriage	507 women with miscarriage in trimester 1 (cases) 908 women with a normal trimester 1 pregnancy (controls)	Interview on intake of coffee, tea, caffeine-containing soda and hot chocolate. Consumption based on women's estimate of cup size	Significant association between caffeine intake of 100-299 and >500 mg/day and miscarriage in women with CYP1B1 Val/Val genotype.	Caffeine (mg/day) 100-299 300-499 >500 Reference: Leu/Leu genotype & <100 mg/day intake	Val/Val genotype 2.63(1.39,4.98) 1.82(0.84,3.93) 3.61(1.36,9.61)	Adjustment for age, smoking, alcohol, previous miscarriage, parity, pregnancy symptoms Unclear when interviews took place
Khoury et al (2004)[16] USA	1978-1993	Wide range including, miscarriage, congenital malformation, pre-eclampsia, delivery at <37wks.	191 pregnant women with type 1 diabetes	Monthly interviews; caffeine consumption based on number cups caffeinated beverages/day	Significant associations observed for spontaneous miscarriage (+ve), pre-eclampsia and infant hypoglycaemia (-ve)	Drinks/day 1-2 ≥3 Reference: 0 drinks/day Caffeine intake at >20 wks gestation	Spont. miscarriage 3.8 (0.8, 16.9) 5.2 (1.2, 22.0) Pre-eclampsia 0.3 (0.1, 1.0) Infant hypoglycaemia 0.2 (0.1, 1.0)	Adjustment for age, yrs since diagnosis of diabetes, nephropathy, retinopathy, glycaemic control, cigarette smoking

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Macono-chie et al (2007)[18] UK	1980-2002	Trimester 1 miscarriage	603 women with most recent pregnancy ending in trimester 1 miscarriage (cases) 6116 women with most recent pregnancy progressing beyond 12 wks (controls)	Questionnaire on reproductive history sent to UK women in 2001. Caffeine intake determined by tea, coffee and caffeinated drink consumption	Apparent association between caffeine intake and risk of miscarriage not significant after adjustment for nausea	Caffeine (mg/day) <151 1.03(0.71,1.49) 151-300 0.93(0.64,1.33) 301-500 1.04(0.72,1.50) >500 1.14(0.79,1.66) Baseline: 0 mg/day	Adjustment for year of conception, maternal age, previous miscarriage, previous live birth and nausea

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Matijas-evich et al (2006)[35] Uruguay	2002-2003	Fetal death	382 women with fetal death ≥20wks gestational age or weighing >350g (cases) 792 women with live term NGA births (controls)	Questionnaire on coffee and mate consumption	Mean caffeine intake significantly higher in cases than controls (156.5 mg/day vs 113.6)	Mean caffeine (mg/day) 1-59 0.74(0.42,1.31) 60-149 0.93(0.51,1.67) 150-299 1.22(0.69,2.17) ≥300 2.33(1.23,4.41) Reference: 0 mg/day	Adjustment for maternal and partner's education, history of miscarriages + fetal deaths, vomiting/ nausea in trimester 1 and attendance for prenatal care
Rasch et al (2003)[13] Denmark	1994	Miscarriage	330 women with miscarriage in gestational wks 6-16 (cases) 1168 women with live fetuses in gestational wks 6-16 (controls)	Questionnaire on daily tea, coffee, cola and chocolate bar consumption during pregnancy	Consumption of ≥ 375 mg caffeine /day associated with increased risk of miscarriage	Caffeine (mg/day) 200-374 1.31(0.92,1.86) ≥375 2.21(1.53,3.18) Baseline: 0-199 mg/day	Adjustment for age, parity, occupation, smoking and alcohol

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Sata et al (2005)[38] Japan	2003-2004	Recurrent pregnancy loss	58 women with two or more miscarriages (cases) 147 women with live births (controls)	Questionnaire on coffee, tea and cola consumption during pregnancy	CYP1A2*1F (AA vs CA CC) genotype found to influence risk	Caffeine (mg/day) 100-299 All women 1.29(0.66,2.50) ≥300 1.82(0.72,4.58) CYP1A2 CC+CA 100-299 1.03(0.42,2.52) ≥300 1.03(0.29,3.70) CYP1A2 AA 100-299 1.94(0.57-6.66) ≥300 5.23(1.05-25.9) Reference: 0-99 mg/day for each grouping	Adjustment for age and smoking status in pregnancy

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Savitz et al (2008)[20] USA	2000-2004	Miscarriage at <20 gestational wks	2407 women recruited at <12 gestational wks	Interview before 16 weeks on caffeine-containing coffee, tea and soda consumption pre-pregnancy, 4 wks after last menstrual period (LMP), + at time of interview or when still pregnant	Coffee and caffeine consumption at all 3 timepoints were unrelated to overall risk of miscarriage.	Caffeine (mg/day) Pre-preg >0-<348 1.6 (0.7,3.4) ≥348-695 1.2 (0.6,2.6) >696 1.1 (0.4,2.6) 4wks post LMP >0-<348 1.2 (0.6,2.2) ≥348-695 1.0 (0.5,2.0) >696 0.5 (0.2,1.4) Time of interview >0-<348 1.1 (0.6,2.2) ≥348-695 1.9 (1.1,3.5) >696 2.3 (1.2,4.5) Reference category: 0 mg/day	Median levels caffeine consumption modest relative to previous studies + authors suggest this restricted the ability to examine effects above 300-400 mg/day Adjustment for maternal age, race ethnicity, maternal education, marital status, alcohol consumption + vitamin use

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Signorello et al (2001)[23] Sweden	1996-1998	Miscarriage	101 women with normal karyotype miscarriages (cases) 953 pregnant women at 6-12 gestational wks (controls)	Interviews within 2 wks of miscarriage or 6 days of enrolment (controls). Coffee, tea, cocoa, chocolate, soft drinks + caffeine-containing medication	Caffeine found to be a significant risk factor among women with low, but not high, CYP1A2 activity. Association with NAT2 genotype less clear.	Caffeine (mg/day) 100-299 ≥300 100-299 ≥300 100-299 ≥300 100-299 ≥300 Reference: 0-99 mg/day for each group	Low CYP1A2 activity 0.32(0.08,1.23) 0.46(0.12,1.73) High CYP1A2 activity 2.42(1.01,5.80) 3.17(1.22,8.22) Slow acetylators 2.38(1.04,5.49) 1.65(0.67,4.06) Fast acetylators 1.07(0.39,2.95) 1.93(0.67,5.51)	Adjustment for age, gestational week, smoking + nausea

Author + location	Study period	Outcome variables	Study sample	Measure of caffeine exposure	Study authors description of results	OR/RR (95% CI)	Comments
Tolstrup et al (2003)[40] Denmark	1991-1995	Miscarriage	303 women from a population-based cohort with miscarriage (cases) 1381 women in cohort who gave birth (controls)	Interview on tea and coffee intake at enrolment into cohort and again 2 yrs later	High pre-pregnancy caffeine intake (>900 mg/day) associated with an increased risk of miscarriage	Caffeine intake pre-pregnancy (mg/day) 75-300 1.26(0.77-2.06) 301-500 1.45(0.87,2.41) 501-900 1.44(0.87,2.37) >900 1.72(1.00,2.96) Reference category: <75 mg/day	Only considers pre-pregnancy caffeine intake Adjustment for age, marital status, smoking and alcohol intake.
Weng et al (2008)[15] USA	1996-1998	Miscarriage at <20 gestational wks	1063 pregnant women recruited at ≤15 gestational wks	Interview on intake of coffee, tea, caffeine-containing soda and hot chocolate	Increasing caffeine consumption associated with an increased risk of miscarriage	Caffeine mg/day <200 1.42(0.93,2.15) ≥200 2.23(1.34,3.69) Baseline: Non-user	Adjustment for maternal age, race, education, family income, marital status, previous miscarriage, nausea and vomiting since LMP, smoking status, alcohol consumption, Jacuzzi use and magnetic field exposure
Wisborg et al (2003)[42] Denmark	1989-1996	Stillbirth and infant death in 1st yr of life	18,478 singleton pregnancies	Questionnaire at approx 16 wks of gestation on coffee intake	Drinking coffee during pregnancy associated with an increased risk of stillbirth but not infant death	Coffee (cups/day) Stillbirth 1-3 0.6 (0.3, 1.1) 4-7 1.4 (0.8, 2.5) ≥8 2.2 (1.0, 4.7) Infant death 1-3 0.9 (0.6, 1.6) 4-7 0.2 (0.1, 0.7) ≥8 1.6 (0.7, 3.6) Baseline: 0 cups/day	Caffeine exposure from tea, cola or drinking chocolate considered insignificant so not included in analysis. Adjustment for smoking and alcohol, parity, age, marital status, BMI, yrs education and employment status in pregnancy

Studies on pre-term birth							
Author + location	**Study period**	**Outcome variables**	**Study sample**	**Measure of caffeine exposure**	**Study authors description of results**	**OR/RR (95% CI)**	**Comments**
Bech et al (2007)[26] Denmark	1998-2002	Birth weight and length of gestation	1207 pregnant women drinking at least 3 cups of coffee/day, recruited before 20 wks gestation	Randomised to drink caffeinated (n=568) or decaffeinated (n=629) instant coffee at usual consumption levels Interviewed throughout pregnancy on daily consumption coffee, tea, cola and cocoa	No significant differences in mean bw or mean length of gestation between caffeinated and decaffeinated groups.	Not reported	Adjustment for length of gestation, parity, prepregnancy BMI and smoking at entry to study. Women were not asked to avoid intake of other caffeinated beverages.
Bicalho and Barros Filho (2002)[27] Brazil	1994-1995	LBW, prematurity and IUGR	354 newborns with bw <2,500 g (cases) 354 newborns ≥3,000 g (controls)	Daily consumption of coffee, tea and soft drinks	No association between caffeine consumption during pregnancy and low birthweight, prematurity and intrauterine growth restriction.	Caffeine (mg/day) Prematurity <300 0.59(0.32,1.09) ≥300 0.32(0.15,0.72)	Abstract only in English. Adjustment for age, schooling, income, marital status, skin colour, parity, smoking, previous lbw child, pre-pregnancy weight, employment status, interval between pregnancies, prenatal care and high blood pressure

Bracken et al (2003)[29] USA	1996-2000	Preterm delivery	2,291 women with singleton live births	Interviews on coffee, tea and soda consumption - Interview on trimester 1 intake conducted before gestation wk 25 - Post natal interview on trimester 3 intake Urine analysis at interview 1	No significant association of caffeine consumption in trimesters 1 or 3 or urinary caffeine with preterm delivery	Trimester 1 Caffeine (mg/Day) 1-149 150-299 ≥300 Reference: average 0 mg/day	Preterm del 1.20(0.80,1.76) 1.74(0.93,3.27) 1.67(0.76,3.81)	Adjustment for age, parity, # prior pregnancies, marital status, race, education, height, smoking in 3rd trimester, weight. Similar ORs reported for caffeine consumption in trimester 3.
Chiaffar-ino et al (2006)[31] Italy	1989-1999	Preterm birth of SGA or normal for gestational age babies	502 women who delivered at <37 wks (cases) 1966 women who gave birth at ≥37 wks	Post pregnancy interview on coffee, tea and cola consumption	No significant association with overall intake of caffeine Inverse association coffee consumption (≥2 servings/day) disregarding caffeine from other sources and risk of SGA preterm babies (OR= 0.5 [0.3,0.8])	Caffeine servings/ day 1 ≥2 1 ≥2 Reference category: 0 servings/day	Preterm SGA 1.1 (0.7,1.8) 1.0 (0.6,1.7) Preterm NGA 0.9 (0.6,1.2) 0.9 (0.7,1.3)	Adjustment for age, education, gestational hypertension and history of preterm birth.
de Souza + Sichieri (2005)[21] Brazil	Not stated	Prematurity	140 newborns with gestational age <37wks (cases) 162 newborns with gestational age ≥37 wks (controls)	'Semi-quantitative' food frequency questionnaire on coffee, tea + powdered chocolate	Total caffeine consumption during pregnancy not associated with prematurity	Caffeine (mg/day) 50-99 ≥100 Baseline: Below 50 mg/day	 1.58(0.32,2.84) 1.35(0.48-3.80)	Abstract only in English Most caffeine intakes were less than 300 mg/day

Studies on teratogenicity							
Author + location	**Study period**	**Outcome variables**	**Study sample**	**Measure of caffeine exposure**	**Study authors description of results**	**OR/RR(95% CI)**	**Comments**
Browne et al (2007)[30] USA	1997-2002	Cardio-vascular malformations (CVMs)	4,196 mothers of infants with cardio-vascular malformation 3,957 controls	Telephone interviews on consumption of caffeinated coffee, tea, soda or soft drinks and chocolate in year prior to pregnancy	No significant positive associations between maternal caffeine consumption and CVMs	Caffeine (mg/day) 10-<100 1.17(0.91,1.50) 100-<200 1.05(0.80,1.38) 200-<300 1.23(0.91,1.66) ≥300 1.24(0.91,1.68) Baseline: <10 mg caffeine/day All CVM	Adjustment for mother's state of residence at time of birth.

Annex A

Search strategy for review of research on reproductive effects of caffeine

Pubmed

Colleagues at the Food Standards Agency's Information Centre searched using the following search terms:

(caffeine OR coffee) AND [("adverse effects" AND "pregnancy") OR "fetal growth restriction" OR "fetal growth retardation" OR "FGR" OR "fetal growth" OR "miscarriage" or "outcomes" OR "birth weight" OR "intrauterine growth retardation" OR "IUGR" OR "small for gestational age" OR "SGA" OR "fetus" OR "preterm birth")]

Limits imposed on search: Published between 2001-2008, limited to 'humans'

Total number of papers: **32**

Of these, 2 papers were not ordered as they were review articles, 2 reported studies performed in rodents, 1 described a study of factors affecting IVF fertility and 6 referred to caffeine only as a confounder in irrelevant studies.

Search conducted on **PubMed** using the following search string:

(caffeine OR coffee) AND ("adverse effects" AND "pregnancy")

Limits imposed on search: Published between 2001-2008, limited to 'humans'

Total number of papers: **88**

This search yielded 24 potentially useful references that were not identified in the previous search. All of the other references in this search were duplicates of those already obtained, or were disregarded primarily as they described studies where pregnancy outcome was not the main focus of the study, or focussed on different species such as primates, rats or mice, or for one of the reasons stated previously.

British Library Inside

Search conducted on **British Library Inside** using the following search string:

(caffeine OR coffee) AND pregnancy

Limits imposed on search: Published ≥2001 only.

Total number of papers: **72**

Of these 18 had not been previously identified. All of the other references in this search were either duplicates of papers already obtained, duplicates within the search, or were disregarded for the reasons outlined above.

Current Contents

Colleagues at the Information Centre searched using the following search terms:

(caffeine OR coffee) AND [("adverse effects" AND "pregnancy") OR "fetal growth restriction" OR "fetal growth retardation" OR "FGR" OR "fetal growth" OR "miscarriage" or "outcomes" OR "birth weight" OR "intrauterine growth retardation" OR "IUGR" OR "small for gestational age" OR "SGA" OR "fetus" OR "preterm birth")]

Limits imposed on search: Published ≥2001 only.

Total number of papers: **175**

From the results of this search only 2 had not been previously identified. Most references were duplicates of those already found and some related to studies conducted in rodents and primates.

From the references (n = 75) obtained, 42 were excluded once the full paper was retrieved: as they were reviews (9), letters in response to papers (7), included in the 2001 COT review (3), studies reporting on maternal health outcomes/fertility (5), reported health issues in young children (6), reporting intake estimates (4), described the use of caffeine for apnoea of prematurity (2), in a foreign language (2), or duplicates (4).