FOREWORD **INTRODUCTION**

CAFEINE

CAS : 58-08-2

SIDS Initial Assessment Report for SIAM 14

(Paris, France, March 2002)

1. Chemical Name:	**Caffeine**
2. CAS No.:	**58-08-2**
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn-Bad Godesberg
4. Shared Partnership With: **5. Roles/Responsibilities of the Partners:**	BASF AG, Germany; Bell Flavors & Fragrances, Inc., United States
• Name of industry sponsor/ consortium.	BASF AG, Germany Contact person: Dr. Hubert Lendle GUP/CL - Z570 D-67056 Ludwigshafen
• Process used.	see next page
6. Sponsorship History • How was the chemical or category brought into the SIDS Program?	by ICCA-Initiative
7. Review Process Prior to the SIAM:	last literature search (update): 24. January 2001 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 18.04.01 and 02.05.01 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms
8. Quality Check Process	As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA.
9. Date of Submission:	01. February 2002
10. Comments:	The peer review of BUA in the toxicology section was mainly based on review articles, including those of the International Agency for Research on Cancer (IARC), and some others. Regarding 'Experience with human exposure: this section of the SIDS dossier is not adequately worked out according to the formal requests of OECD manual for investigation of HPV chemicals. However, the

	lead company BASF AG has assured us of its willingness to amend those points as and if requested by the OECD members.

OEC

D/ICCA - The BUA* Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- **a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET**

- **Review of data and assessment of the quality of data**

- **Review of data evaluation**

- **Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications**

- **Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications**
  (if original reports are missing: reliability (4) not assignable)

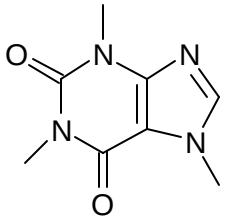
- **Review o f validity of structure -activity relationships**

- **Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)**

In case of data gaps, review of testing plan or rationale for not testing.

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	58-08-2
Chemical Name	Caffeine
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Animal data

In animals studies caffeine showed acute toxicity LD50 rat oral 200-400 mg/kg bw, LD50 mouse oral 185 mg/kg bw, LC50 rat inhalative ca. 4.94 mg/l/4h; LD50 rat dermal > 2000 mg/kg bw). The undiluted substance was not irritating to the eyes of rabbits, the substance in a 50% aqueous dilution was not irritating to the skin of rabbits. In a 90-day-drinking water study in rats and mice a slight decrease of body weight gain was observed. No clinical signs of toxicity and significant gross lesion or microscopic findings were seen in either rats or mice. The NOAEL for rats was 1500 ppm (ca. 151-174 mg/kg bw/day) and for mice 1500 ppm (ca. 167-179 mg/kg bw/day). In all dose groups effects on salivary glands were observed, which were regarded as an adaptive and reversible response to the sympathomimetic effect of caffeine. There are numerous studies available concerning genetic toxicity *in vitro* and *in vivo*. In the majority of the studies caffeine produced negative results. Several positive responses were obtained only in studies which used extreme culture conditions, lethal doses or non-validated methods. There was no statistically significant increase in the tumor incidence in treated animals as compared to controls even at doses exceeding the maximum tolerated dose and given to rats over a major portion of their lifespan.

Caffeine resulted in reproductive effects occurring in the presence of general toxicity in parental rats and mice. A NOAEL in rats was not established. NOAEL: mouse 22 mg/kg bw/d (F0 parental, F1 offspring), 88 mg/kg bw/d (F1 parental, F2 offspring).

Gross malformations were observed in rats and mice only after bolus administration (i.p. or gavage) of very high maternal toxic doses. Fetotoxicity without maternal toxicity was observed in one drinking water study. NOAEL: 360 ppm (51 mg/kg bw/d) (maternal), 70 ppm (10 mg/kg bw/d) (fetotoxicity), 2000 ppm (205 mg/kg bw/d) (teratogenicity). However, in two other gavage studies with lower doses this finding was not confirmed. No NOAEL for maternal toxicity could be established; the NOAEL for developmental toxicity was 40 mg/kg bw/d; no teratogenic effects were observed.

Experience with human exposure

Absorption from gastrointestinal tract is rapid. Peak plasma levels are reached after 15 to 120 minutes after ingestion. The elimination half-life in adults is about 2.5 to 4.5 hours. A small percentage is excreted in bile, salvia, semen and breast milk. In both humans and rats, excretion mainly occurs via urine (about 90 % dose in rats; > 95 % in humans).

Caffeine metabolism is qualitatively similar in animals and humans. The main metabolic pathways are: demethylation and hydroxylation of the 8-position leading to the formation of the respective uracil and uric acid derivatives. There are, however, some quantitative differences in the metabolic profile.

Low doses (up to 2 µg/ml in blood) stimulate the central nervous system, while high blood concentrations (10-30 µg/ml) produce restlessness, excitement, tremor, tinnitus, headache, and insomnia. Caffeine can induce alterations in mood and sleep patterns, increase diuresis and gastric secretions. Acute toxicity is rare and is the result of an overdose. Lethal dose is estimated to be 5 g.

Caffeine and coffee consumption are highly correlated in most populations studied; thus it is difficult to separate the two exposures in epidemiologic investigations. No association between moderate consumption of coffee/caffeine and cardiovascular diseases was demonstrated in more recent studies. In short-term clinical trials an increase in blood pressure was seen, whereas in other surveys no relationship between caffeine consumption and elevation of blood pressure was observed. Caffeine consumed in moderate amounts did not cause persistent increase in blood pressure in normotensive subjects. Effect on cardiac rhythm is still in debate. Small increase in calcium excretion associated with coffee/caffeine intake was seen in subjects with dietary calcium deficiency. Caffeine has weak reinforced properties, but with little or no evidence for upward dose adjustment, possibly because of the adverse effects of higher doses. Withdrawal symptoms, although relatively limited with respect to severity, do occur, and may contribute to maintenance of caffeine consumption. Caffeine use is not associated with incapacitation. There is little evidence for an association of caffeine intake and benign breast disease. No association was found in a study with biopsy-confirmed controls.

A cohort study with short follow-up period showed no association between caffeine consumption and mortality from cancers at all sites. Case control studies of breast cancer showed no association with caffeine intake. Weak positive associations between caffeine intake and lung, bladder or pancreas cancer as well as a weak inverse association between caffeine intake and colon cancer may be due to bias or confounding. IARC evaluated that there is inadequate evidence of carcinogenicity in humans.

There are conflicting reports on the effect of caffeine on human reproduction. A teratogenic effect has not been proven. While caffeine intake up to 3-4 cups/day or 300 mg caffeine/day is unlikely to be causally related to spontaneous abortions or relevant reduction of birth weight, an association between higher daily caffeine intake and these endpoints can not be excluded. Conflicting results exist regarding a potential relationship between caffeine/coffee consumption and delayed conception or infertility.

Environment

Caffeine has a water solubility of 20 g/l, a vapor pressure of $4.7 * e^{-6}$ Pa and a log Kow of – 0.091.

Distribution modelling using Mackay, Level I, indicates that the main target compartment will be water with 99.99%.

Concerning biodegradation there is only a not valid study available for caffeine. However, from the structurally analogous compound theophylline it can be concluded that caffeine is readily biodegradable. The calculated hydrolysis rate is extremely slow. In the atmosphere caffeine will be indirectly photodegraded by reaction with hydroxyl radicals with a half-life of 19.8 hours (calculated).

Bio- and geoaccumulation are not expected according to the log K_{ow} (-0.091).

The acute aquatic toxicity has been determined for fish (*Leuciscus idus* LC50(96h) 87 mg/l), for aquatic invertebrates (*Daphnia magna* EC50(48h) 182 mg/l) and for algae (*Scenedesmus subspicatus* ErC50 (72h), ErC10 (72h) >100 mg/l). Results from prolonged or chronic studies are not available. Following the EU risk assessment procedure the PNEC aqua can be calculated to 0.087 mg/l by applying an assessment factor of 1000 on the most sensitive species (*Leuciscus idus* LC50(96h) 87 mg/l).

Exposure

Caffeine is produced with a volume of 10,000 to 15,000 tons per year, world-wide, including 3,000 to 4,000 tons of natural caffeine. It is mainly used in the food and pharma sectors.

Furthermore caffeine is a naturally occurring substance in various plant species (e.g. 0.9 to 2.6% in green coffee beans). It is a component in coffee, tea and cocoa. The use in food will be the predominant way of human exposure and of exposure of the environment.

Production sites for the technical product: EU (Germany) 1, NAFTA 2, Japan 1, India 4 and China 10. Production sites for natural caffeine are appr. 7 to 8 worldwide, thereof 4 in Europe.

Exposure to workers during production is adequately controlled by the use of engineering controlled methods in the industry of the sponsored country.

Workplace measurements during filter changes (Germany) : 0.1- ca. 1.2 mg/m^3 (8h).

At the German production site, process waters with relevant substance quantities are separated and combusted.

NATURE OF FURTHER WORK RECOMMENDED

Environment: No recommendation for further work, because the substance is readily biodegradable, has a low bioaccumulation potential and is only moderately toxic to aquatic organisms.

Human Health: No recommendation for further work for the following reasons:

The pharmacological properties of caffeine are well known. There are many studies relevant to reproductive toxicity; some suggest an adverse effect but the total data base is inconsistent. The case of caffeine is regulated by food and drug agencies of national governments.

FULL SIDS SUMMARY

CAS NO: 58-08-2		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			235 – 239 °C
2.2	Boiling Point			Sublimation at 178 °C
2.3	Density			1.23 g/cm^3 at 18 °C
2.4	Vapour Pressure		calculated	0.0000047 Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		measured	-0.091 at 23 °C
2.6	Water Solubility			20.000 mg/l at 20 °C
	pH			5.5 – 6.5 at 10 g/l and 20 °C
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		calculated	Indirect photolysis: air Reaction with OH-radicals: $t_{1/2}$ = 19.8 hours
3.1.2	Stability in Water		calculated	$t_{½}$>1 year
3.2	Monitoring Data			
3.3	Transport and Distribution		Mackay level I calculation	In Water 99.99 % In sediment, soil and biota <<0.1%
3.5	Biodegradation			readily biodegradable, estimated from ready biodegradability of structurally analogous compound theophylline
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	Leuciscus idus	DIN 38 412 part 15	LC_{50} (96 hours) = 87 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates	Daphnia magna	EG 79/831, Annex V, part C	EC_{50} (48 hours) = 182 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	Scenedesmus subspicatus	OECD 201	EC_{50} (72 hours) >100 mg/l
4.4	Toxicity to bacteria	Pseudomonas putida	DIN 38412 part 8, draft	EC_{50} (17 hours) = 3,490 mg/l
4.6.2	Toxicity to terrestrial plants	Oryza sativa		Growth inhibition at 0.5 – 10 mM
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)	Red-winged blackbird		LD_{50} = 316 mg/kg
		Starling		LD_{50} >500 mg/kg
		Tribolium castaneum		LD_{50} adults (20 days) = 288 mg/kg LD_{50} larvae (20 days) = 251 mg/kg

CAS NO: 58-08-2		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Comparable to OECD guideline 401	LD50 261-383 mg/kg bw
		Rat	NTP program	LD50 200-400 mg/kg bw
		mice	NTP programm	mice 185 mg/kg bw
5.1.2	Acute Inhalation Toxicity	Rat	OECD 403	Ca. 4.94 mg/l/4h, aerosol
5.1.3	Acute Dermal Toxicity	Rat	Comparable to OECD guideline 402	> 2000 mg/kg bw
5.4	Repeated Dose Toxicity	Rat	90 days, drinking water, NTP program,	NOAEL 1500 ppm (174 mg/kg bw/d females, 151 mg/kg bw/d males)
		Mouse	90 days, drinking water, NTP program	NOAEL 1500 ppm (179 mg/kg bw/d females, 167 mg/kg bw/d males)
5.5	Genetic Toxicity *In Vitro*			
A.	Bacterial Test (Gene mutation)	*Salmonella typhimurium*	Comparable to OECD guideline 471	Negative (with and without metabolic activation)
B.	Non-Bacterial *In Vitro* Test (Chromosomal aberrations)	CHL cells	Comparable to OECD guideline 473	Positive (only without metabolic activation tested)
		Human lymphocytes	Comparable to OECD guideline 473	Negative (with and without metabolic activation)
5.6	Genetic Toxicity *In Vivo*	Rat	Cytogenetic, feed, 117 weeks	Negative
		Mouse	Cytogenetic, oocytes, i.p.	Negative
		Mouse	Cytogenetic, spermatogonia, i.p. Comparable to OECD guideline 483	Negative
		Mouse	Micronucleus, i.p. Comparable to OECD guideline 474	Negative
		Mouse	Micronucleus, gavage Comparable to OECD guideline 474	Weak positive in the highest dose
		Mouse	Dominant lethal test, drinking water or gavage	Negative
		Mouse	Host-mediated assay with E. coli	Negative
5.8	Toxicity to Reproduction	Rat	Continuous breeding, task 1-4	NOAEL parental/F1 not established (reduced body weight gain in all treated groups)
		Mouse	Continuous breeding , task 1, 2, 3	NOAEL Parental/ F1 offspring = 22 mg/kg bw/d
		Mouse	Continuous breeding, task 1, 2, 4	NOAEL Parental/ F1 offspring = 22 mg/kg bw/d NOAEL F2 offspring = 88 mg/kg bw/d

5.9	Developmental Toxicity/ Teratogenicity	Rat	Drinking water day 0-20	NOAEL maternal = 51 mg/kg bw/d NOAEL fetotoxicity = 10mg/kg bw/d NOAEL teratogen > 205 mg/kg bw/d
		Rat	Gavage, day 1-20, NTP program	LOAEL maternal 40 mg/kg bw/d NOAEL fetotoxicity = 40 mg/kg bw/d NOAEL teratogen = 80 mg/kg bw/d
		Rat	Gavage, day 1-20,allowed to deliver, NTP programm	LOAEL maternal: 10 mg/kg bw/d NOAEL fetotoxicty: 40 mg/kg bw/d NOAEL teratogen: 40 mg/kg bw/d
Further Data	Corrosiveness/Irritation Skin	Rabbit	OECD 404	Not irritating
	Corrosiveness/Irritation Eye	Rabbit	OECD 405	Not irritating
	Sensitisation	Guinea Pig	No data	
	Carcinogenicity	Rat	Drinking water up to 2000 ppm, 104 weeks	Negative
5.11	Experience with Human Exposure		Kinetic, Metabolism	Rapid absorption from gastrointestinal tract; peak plasma levels reached after 15 to 120 minutes. Elimination half-life 2.5 to 4.5 h. Metabolized by hepatic microsomal enzymes (demethylation, 95 %). In both humans and rats, excretion mainly occurs via urine (about 90 % dose in rats; > 95 % in humans). Caffeine metabolism is qualitatively similar in animals and humans. The main metabolic pathways are: demethylation and hydroxylation of the 8-position leading to the formation of the respective uracil and uric acid derivatives. There are, however, some quantitative differences in the metabolic profile.
			Toxicity	Low doses (up to 2 µg/ml in blood): stimulation of the central nervous system; high blood concentrations (10-30 µg/ml): restlessness, excitement, tremor, tinnitus, headache, and insomnia. Alterations in mood and sleep patterns, increase diuresis and gastric secretions. Lethal dose: 5 g (overdosing).
			Epidemiology	Caffeine and coffee consumption are highly correlated in most populations studied; thus it is difficult to separate the two exposures in epidemiologic investigations. Bias or confounding has to be taken into account in many of the studies.
			Cardiovascular	No association between moderate consumption of coffee/caffeine and cardiovascular diseases. Caffeine consumed in moderate amounts did not cause persistent increase in blood pressure in normotensive subjects. Short-term clinical studies have shown that in caffeine-naive subjects, 250 mg of caffeine increased systolic

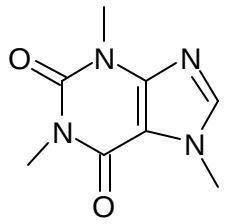
				blood pressure. Effect on cardiac rhythm in debate.
			Other effects	Small increase in calcium excretion in subjects with dietary calcium deficiency. Weak reinforced properties, limited withdrawal symptoms, not associated with incapacitation. Little evidence for an association with benign breast (no evidence in biopsy-confirmed studies).
			Carcinogenicity	No association with mortality from cancers at all sites. No association with breast cancer. Weak association with bladder cancer. Effect on colon and pancreas in debate. IARC evaluated that there is inadequate evidence of carcinogenicity in humans.
			Reproductive toxicity	Conflicting reports on the effect of caffeine on human reproduction. Teratogenic effect has not been proven. High exposure (consumption of >3-4 cups of coffee/day or 300 mg caffeine/day) may result in birth weight reduction. No final conclusion for an association between prematurity or spontaneous abortion. Conflicting results exist regarding a potential relationship between caffeine/coffee consumption and delayed conception or infertility.

SIDS Initial Assessment Report (SIAR)

1 IDENTITY

Chemical Name: Caffeine
Synonyms: 1,3,7-trimethyl-2,6-dioxopurine
1,3,7-trimethylxanthine
3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione
7-Methyltheophylline

CAS Number: 58-08-2
Empirical Formula: $C_8 H_{10} N_4 O_2$
Structure:



General Substance Information

Substance type: organic, natural substance
Physical status: solid
Purity: 98.5 - 100 % w/w

Physical and chemical properties

Caffeine is soluble in water with 20 g/l at 20°C (BASF AG, 2001a) and has a calculated vapour pressure of 0.0000047 Pa at 25°C (BASF AG, 2000a). The Henry´s law constant has been estimated to $1.9*10^{-19}$ atm*m^3/mole (Swann et al., 1983). The partition coefficient log P_{ow} is measured to –0.091 at 23°C (BASF AG, 1988a). The density of caffeine is higher than that of water (1.23 g/cm^3 at 18°C) (The Merck Index, 1989, CRC Handbook of Chemistry and Physics; 1991-1992). The melting point is 235 – 239 °C (BASF AG, 2001a), Caffeine sublimes at 178°C (The Merck Index, 1989).

2 GENERAL INFORMATION ON EXPOSURE

1999 the estimated world production amounts to 10,000 – 15,000 tons including 3,000 to 4,000 tons of natural caffeine (Europe 5,000 – 10,000 t/a, Germany 1,000 – 5,000 t/a).
Production sites for the technical product:
EU (Germany) 1, NAFTA (USA, Canada, Mexico) 2, Japan 1, India 4 and China 10.
Production sites for natural caffeine are appr. 7 to 8 worldwide, thereof 4 in Europe.

Caffeine is a substance with wide disperse use. It is predominantly used in the food sector and pharma sector (80% and 16% rsp.). A smaller part is used in cosmetics (3%) or in technical applications (1%).
Furthermore caffeine is a naturally occurring substance in various plant species (e.g. 0.9 to 2.6% in green coffee beans). It is a component in coffee, tea and cocoa. The use in food will be the predominant way of human exposure and of exposure of the environment.
In the Danish Product register (Aug. 2001) there are 6 products containing caffeine. Product types are food/feedstuff flavourings and nutrients and laboratory chemicals.

2.1 Environmental exposure and fate

Measured data on emission into the atmosphere or into surface water via waste water treatment plants are not available. At the German production site, process waters with relevant substance quantities are separated and incinerated (BASF AG, 2001c).

Distribution modelling using Mackay, Level I (V 2.1), indicates that the main target compartment will be water with 99.99% (BASF AG, 2000a).

Caffeine is indirectly photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 19.8 hours (calculated) (BASF AG, 2000a). Concerning biodegradation there is only one test report available (Henkel KgaA, 2000). In this test that was performed according to OECD 301 F two parallel vessels were used. In one vessel a biodegradation of 58 % and in the other of 84 % was found. As the two parallel vessels differ by more than 20 %, the validity criteria for the test are not fulfilled and the test has to be regarded as not valid. However, for the structurally analogous substance theophylline (CAS No: 58-55-9) there is a test on ready biodegradability available from which it can clearly be concluded that this substance is readily biodegradable (OECD 301 A, 90 - 100 % after 22 days, >90% at the end of the 10-days-window) (BASF AG, 2000b). As the two substances differ only by one methyl group it can be concluded with high probability that also the substance caffeine is readily biodegradable. This is confirmed by Richardson and Bowron (1985). They gave in a review report the information that caffeine is readily biodegradable. However, as no further information is given on the test that was performed and the exact results, this information cannot be validated. The calculated hydrolysis rate is extremely slow ($T_{1/2}$ >1 year) (BASF AG, 2000a).

The estimated soil adsorption coefficient (log K_{oc} –0,0135) suggests that caffeine would not absorb to soil particles (BASF AG, 2000a). No experimental data on bioaccumulation are available. The log K_{ow} of -0.091 indicates no potential for bioaccumulation (BASF AG, 1988a).

2.2 Human Exposure

Exposure of workers to caffeine during production is adequately controlled in the industry of the sponsor country (Germany).

Caffeine is produced under controlled conditions in closed systems. Exposure may only occur during occasional filter changes. In the bottling plant local exhaused systems are used. During filter changes, dust masks, throw away protective suits, and gloves are worn. Hence, there is practically no exposure under normal workplace conditions.

Workplace measurements (during filter changes), Germany: 0.1- ca. 1.2 mg/m3 (8h)

3 HUMAN HEALTH HAZARDS

3.1 Effects on human health

In the human health section many review articles have been used, to which a Klimisch Code 4 (secondary literature) was assigned, but which was felt adequate for the assessment of a substance with a huge amount of data.
Remark: The scientific literature of caffeine comprises a lot of published studies and reviews due to its containment in beverages (coffee, tea, cocoa, cola drinks, etc.) and its use as pharmaceutical. With a focus on health and safety issues comprehensive reviews including those of the International Agency for Research on Cancer (IARC), 1991 and Nehlig and Debry, 1996 and *Christian and Brent, 2001* studies cited in these reviews were choosen for the robust summary of caffeine. For selected endpoints (e.g. chronic, carcinogenic, reproductive toxicity) additional up-date retrieval was done.

Caffeine and coffee consumption are highly correlated in most of the populations studies; thus, it is very difficult to separate the two exposures in epidemiological studies. It was therefore not possible to evaluate adequately the effect of caffeine per se. Most of the studies examined the relationship between drinking cups of coffee per day and reproductive effects. The caffeine consumption by other sources as tea and cola as well as quantitative differences between various types of coffee often have not been considered appropriately.
Thus, the impact of potentially both differential and non-differential misclassification cannot be addressed adequately. It is often not even clear whether the true effect has been over- or underestimated.
In several studies potentially confounding factors such as alcohol, smoking, socioeconomic status, working conditions have not been taken into account. Under these circumstances weak to moderate associations might be pretended.

3.1.1 Experience with human exposure

3.1.1.1 Toxicokinetics and metabolism

Kinetics
In humans caffeine is readily absorbed from the gastrointestinal tract *(Chvasta and Cooke, 1971, Marks and Kelly, 1973, Bonati et al., 1982, Blanchard and Sawers, 1983)*. Caffeine is bound to plasma proteins at levels of 10-30 % at a wide range of concentrations *(Bonati and Garattini, 1984)*. After oral doses of 5-8 mg/kg bw, peak plasma concentrations of 8-10 µg/ml were reached *(Bonati et al., 1982, Blanchard and Sawers, 1983, Arnaud, 1987)*.
Peak plasma concentrations are reached in 15-120 minutes in humans and animals *(Bonati et al., 1982, Arnaud and Welsch, 1982)*, and half-lives of 2.5-4.5 hours were observed in humans and 2.5 h in rats receiving a 4.0 mg/kg dose of caffeine.
Caffeine is eliminated by first order kinetics from humans *(Bonati et al., 1982)*. Caffeine half-life is increased in the neonatal period due to the immaturity of hepatic enzyme systems *(Aranda et al., 1979, Parsons and Neims, 1981)*. It is also prolonged during the last trimester in pregnant women *(Brazier et al., 1983)*, and in women taking oral contraceptives *(Patwardhan et al., 1980, Abernethy and Todd, 1985)*. The clearance of caffeine is stimulated by smoking *(Parsons and Neims, 1978, Jores et al., 1988)*.
Caffeine is distributed relatively uniformly throughout all body tissues, including cerebrospinal fluid, breast milk, salvia, and semen *(Goldstein and Warren, 1962, Somani et al., 1980, Beach et al., 1982, Rodopoules and Norman, 1996)*. The volume of distribution is about 0.7 l/kg bw *(Arnaud, 1987)*.

The elimination of caffeine occurs through metabolism by hepatic microsomal enzyme systems *(Grant et al., 1987),* and elimination is impaired in the presence of liver disease *(Statland et al., 1976).* Only a small percentage is excreted unchanged in the urine *(van der Merwe et al., 1988).* Caffeine crosses easily the placental barrier *(Somani et al., 1980).*
In both humans and rats, excretion mainly occurs via urine (about 90 % of the dose in rats; > 95 % in humans) (*Arnaud, 1993*).

Metabolism
Caffeine metabolism is qualitatively relatively similar in animals and humans *(Arnaud, 1993)*. The main metabolic pathways are: demethylation and hydroxylation of the 8-position leading to the formation of the respective uracil and uric acid derivatives. There are, however, some quantitative differences in the metabolic profile. Humans are characterized by the importance of 3–methyl demethylation leading to the formation of paraxanthine and especially metabolites thereof through subsequent metabolic steps. The main urinary metabolites in humans are 1-methyluric acid, 1-methylxanthine, 5-acetylamino-6-formylamino-3-methyluracil (not found in rats and mice), 1,7-dimethyluric acid and paraxanthin. In rats and mice, the metabolism of caffeine is predominantly via theobromine and theophylline. The main urinary metabolites are 1,3-dimethyluracil, paraxanthine, trimethyluric acid, theophylline, and theobromine. Caffeine metabolism decreases during pregnancy, resulting in higher serum concentrations.

3.1.1.2 Toxic effects (poisoning, overdosing)

Only rare deaths from overdosage of caffeine have been reported *(Gilbert, 1976).* It has been estimated that 5 g to 10 g may be fatal in man (total dose, appr. 65 cups of coffee taken at one time*) (Krantz and Carr, 1951, Rivenes, 1997)*. Blood concentrations of 10-30 µg/ml may produce restlessness, excitement, tremor, tinnitus, headache and insomnia, low doses (up to 2 µg/ml in blood) stimulate the central nervous system *(Ashton, 1987, Stavric, 1988).* Some adverse effects like gastric symptoms, insomnia, seizure, and fever were reported after overdosing (appr. 750 mg in an adult) (*Lachance, 1982, Stavric, 1988, FitzSimmons and Kidner, 1997, Daroca et al., 1996).*

3.1.1.3 Chronic effects

3.1.1.3.1 Cardiovascular disease
No association between increased caffeine consumption and increased mortality due to cardiovascular disease was found *(Martin et al., 1988).*
Earlier studies suggested an association of caffeine consumption of more than 6 cups of coffee with coronary heart disease (CHD) *(Paul et al., 1963, Boston Collaborative Drug Surveillance Program, 1972, Jick et al., 1973)*. In more recent years, retrospective *(Hennekens et al., 1976, Rosenberg et al., 1980, Willett et al., 1996)* and prospective studies have consistently failed to demonstrate an association between caffeine and CHD *(Yano et al., 1977, Heyden et al., 1978, Murray et al., 1981, Welin et al., 1984, Grobbee et al., 1990, Rosengren and Wilhelmsen, 1991, Hart et al., 1997*). In a case-control study neither caffeinated nor decaffeinated coffee (drinking ≥4 cups/day of caffeinated coffee compared to drinking ≤1 cup/week, resp. ≥1 cup/day of decaffeinated coffee compared to nondrinkers) was associated with the risk of myocardial infarction *(Sesso et al., 1999).*

3.1.1.3.2 Hypertension
Short-term clinical studies have shown that in caffeine-naive subjects, 250 mg of caffeine increased systolic blood pressure *(Robertson et al., 1978, Ammon et al., 1983).* In a cross-sectional study of 30,000

middle aged men consuming caffeine showed an inverse association with systolic and diastolic blood pressure *(Stensvold et al., 1989)*. Similar findings were reported in a multiple risk factor intervention trial *(Stamler et al., 1997)* and in a cross-sectional study *(Periti et al., 1987)*. Surveys of the general population demonstrated a positive correlation between caffeine consumption and systolic but not diastolic blood pressure *(Lang, et al. 1983a, Lang et al., 1983b)*. No relationship between increasing caffeine consumption and elevations of blood pressure was seen in large cross-sectional study in employees *(Bertrand et al., 1978)*. An immediate dose-related difference in systolic and diastolic blood pressure were seen in healthy nonsmokers *(Lane et al., 1998)* and in hypertensive patients *(Rachima-Maoz et al., 1998)*.

Though consumption of caffeine (eight cups of regular coffee corresponding to 500 mg caffeine per day) may exhibit acute increases in blood pressure, the long-term effects appear to be minimal. After one to four days of regular consumption a tolerance develops, with blood pressure returning to previous levels.

3.1.1.3.3 Arrhythmias

Heavy coffee consumption (≥ 9 cups/day) was associated with more than twice the likelihood of ventricular premature beats in a population survey *(Prineas et al., 1980)*. However, *Sutherland et al., 1985, Roberston et al., 1981, Myers et al., 1987, Newsby, 1996* reported that caffeine doses up to 500 mg/day do not affect cardiac rhythm in normal subjects and patients.

3.1.1.3.4 Lipids, glucose

Experimental studies do not reflect a caffeine effect on blood cholesterol. Changes in blood cholesterol are similar in individuals consuming decaffeinated coffee or regular coffee *(van Dusseldrop et al., 1990, Superko et al., 1991)*. Blood cholesterol levels were also comparable in subjects given placebo or 600 mg caffeine *(Herbert et al., 1987)*. A meta-analysis of randomized controlled clinical trials showed increased serum lipids in studies of patients with hyperlipidemia and in trials of caffeinated or boiled coffee. Trials using filtered coffee demonstrated very little increase in serum cholesterol. Consumption of unfiltered, but not filtered, coffee increases serum levels of total and LDL cholesterol (*Jee et al., 2001*). An insulin independent rise in blood glucose was seen in subjects receiving 200 mg caffeine *(Pizziol et al., 1998)*.

3.1.1.3.5 Calcium metabolism

Increased urinary and fecal excretion of calcium and other minerals associated with dietary caffeine have been reported *(Massey and Wise, 1984, Massey and Opryszek, 1990, Whiting, 1990)*. Although caffeine caused a small positive increase in urinary calcium excretion, it did not affect overall bone density *(Lloyd et al., 1991)*. Negative findings with respect to caffeine intake, bone mineral content, and risk of fractures were reported *(Johansson et al., 1992, Harris and Dawson-Hughes, 1994, Kreiger et al., 1992, Lloyd, 1997)*. Other reports suggested that consumption of more than 2 cups of coffee a day may be associated with an increased risk of hip fracture *(Kiel et al., 1990, Hernandez-Avila et al., 1991)*. However moderate caffeine intake (100 mg/day) appears not be associated with significant reduction in bone gain *(Packard and Recker, 1996, Lloyd et al., 1998)*.

3.1.1.3.6 Fibrocystic breast disease

There is little evidence to support an association between caffeine intake (up to 6 cups of coffee and more per day) and an increase in the incidence of benign breast disease or an affection of its course when this condition is present (*Levinson and Dunn, 1986, Lawson et al., 1981, Marshall et al., Heyden and Fodor, 1986, Lubin et al., 1985, Rohan et al., 1989)*.

3.1.1.3.7 Tolerance and withdrawal

Case reports and clinical studies of caffeine withdrawal most frequently reported symptoms of abrupt withdrawal as mild to moderate headache beginning 12-24 hours after terminating intake (300 mg/day) and lasting up to a week *(Griffiths and Mumford, 1995, Griffiths and Woodson, 1988, Evans and Griffiths, 1992*). Decreased responsiveness to daily caffeine (500 mg/day) administration with respect to blood pressure *(Ammon et al., 1983, Roberston et al., 1981),* diuresis (minimal effectiv diuretic dose 70 mg/day) *(Eddy and Downs, 1928),* and plasma epinephrine, norepinephrine, and plasma renin activity (250 mg/day) *(Robertson et al., 1978),* but not to the effect of caffeine on urinary calcium excretion (300 mg/day) was reported *(Massey and Opryszek, 1990).* No effect on mood and alertness was seen after single caffeine dose (600 mg/day) *(Sicard et al., 1996)* or withdrawal (300 mg/day) *(Comer et al., 1997).* Other studies on caffeine deprivation found an association with decreased vigor and performance on reaction and increased fatigue (250 mg/day) *(Phillips-Bute and Lane, 1998, Bernstein et al., 1998).*

3.1.1.4 Carcinogenicity

Heavy coffee consumption tends to be associated with other risk factors for various types of cancer, e.g. smoking, alcohol, physical inactivity (*Giovannucci, 1998*). Residual confounding might explain weak positive associations between caffeine consumption and lung, bladder, or pancreas cancer.

Based on the currently available literature *Nehlig and Debry's* (*1996)* conclusion that in the doses usually consumed by man, coffee does not have any potential carcinogenic effect can still be supported.

Whether the consumption of doses higher than 4 mg/kg/day slightly enhances or lowers the risk for some cancer types is currently not clear.

The IARC evaluates the carcinogenicity in humans of caffeine as inadequate evidence (IARC 1991).

3.1.1.4.1 Different sites

The effect of caffeine consumption (av. 317 mg/day) on mortality was evaluated in a historical cohort study of 10,064 diagnosed hypertensive individuals participating in the Hypertension Detection and Follow-up Program from 1973 to 1979. No evidence was found for an association between increased level of caffeine consumption (up to > 428 mg/day) and increased cancer mortality during the following four years *(Martin et al., 1988).*

3.1.1.4.2 Breast

Several case-control studies provided no association between coffee intake (up to ≥ 7 cups/day) and breast cancer risk *(IARC, 1991).* Also new case-control studies confirmed this result *(Hunter, 1992, McLaughlin et al., 1992, Folsom et al., 1993, Levi et al., 1993, Smith et al., 1994, Tavani et al., 1998).*

3.1.1.4.3 Colon

Cohort studies that addressed the issue of coffee drinking (up to ≥3 cups/day) and risk of cancer of the colon have generally been interpreted as showing no association. There are case-control studies that indicated inverse associations and others find a risk. Bias and confounding could not be excluded as the source of the apparent associations *(IARC, 1991*). In recent case-control and cohort studies no increased risk of colorectal cancer from caffeine intake (up to ≥7 cups/day) was found *(Cipriani and Geddes, 1996, Giovannucci, 1998, Hartman et al., 1998, Tavani et al., 1997).* The lower risk of colorectal cancer with high vs. low coffee consumption as determined in the meta-analysis by *Giovannucci (1998)* might be due to an avoidance of coffee by unidentified high-risk individuals, or due to enhanced colonic motility induced by coffee, or due to antimutagenic components in coffee (not necessarily caffeine).

3.1.1.4.4 Bladder

In cohort studies on coffee consumption neither an increase nor a decrease risk for bladder cancer was found. Several case-control studies showed a weak positive association, while others did not. Taken as a whole, the data are consistent with a weak positive relationship between coffee consumption (up to >5 cups/day) and the occurrence of bladder cancer, but the possibility that this is due to bias or confounding cannot be excluded *(IARC, 1991)*.

3.1.1.4.5. Non-Hodgkin lymphoma, lung, pancreas

Cohort studies on the relationship between coffee consumption and pancreatic cancer did not report a significant association with increased consumption; any nonsignificant increase was reduced after adjustment for smoking. In an early case-control study a positive relationship between coffee consumption (up to ≥5 cups/day) and pancreatic cancer was reported. Several subsequent reports (coffee intake ≥7 cups/day) have been less positive overall. Potential biases associated with the comparability of case and control groups also complicate interpretation, and methodological problems were noted in some studies *(IARC, 1991)*. A recent case-control study showed a U-shaped dose-response relationship between coffee intake (never, occasionally, and 3+ cups/day) and the relative risk for pancreatic cancer, suggesting a preventive effect of small amounts of coffee. However, the authors did no present data to verify this suggestion (*Nishi et al., 1996)*.

In a case-control study no association between coffee consumption (up to 4 cups/day , resp. 2 or more cups/day) and non-Hodgkin´s lymphoma was found (Tavani et al., 1994). Concerning lung cancer, there have been reports of studies showing no or weak associations with the consumption of caffeine-containing drinks (*Mendilaharsu et al., 1998*, and others quoted by *Mendilaharsu et al., 1998, Jacobsen et al., 1986)*. Data are inadequate for an assessment.

3.1.1.5 Effects on reproduction

Christian and Brent, 2001 concluded in their recent review on reproductive and developmental risks of caffeine that the usual range of human exposures to caffeine from food and beverages is below the threshold dose that would result in developmental/teratogenic or reproductive effects.

With regard to the endpoints low birth weight and spontaneous abortion, some studies of good quality and power have suggested an increased risk with higher coffee consumption (mostly more than 300 mg/day). Therefore, these endpoints will be addressed more in detail while the evidence of other adverse effects can be considered as inadequate based on the presently available data.

3.1.1.5.1 Delayed conception and infertility

Delayed conception was reported in association with coffee consumption of four to seven cups/day or caffeine consumption as little as 100 mg/day (total dose) *(Christianson et al., 1989, Wilcox et al., 1988, Williams et al., 1990, Hatch and Bracken, 1993, Stanton and Gray, 1995, Bolumar et al., 1997, Curtis et al., 1997)*. These findings were not confirmed in other studies *(Riduan Joesoef et al., 1990, Hakim et al., 1998, Jensen et al., 1998)* or a slight association was only seen in women who smoked and also consumed at least 8 cups of coffee per day *(Olsen, 1991)*. Lack of information on confounder like female body mass index, hormonal status, disease of female reproductive organs, semen quality, frequency of intercourse, especially in the studies reporting delayed conception, suggests that these findings need further verification.

Risk of infertility due to tubal disease or endometriosis was observed in women consuming upper levels of caffeinated beverages (more than 7 g/month) (*Grodstein et al., 1993)*. No significant association between consumption of caffeinated beverages, except tea, and infertility was found in a prospective study *(Caan et al., 1998)*.

3.1.1.5.2 Low birth weight

Several studies assessing coffee, tea and cola consumption to estimate caffeine intake have shown an association between maternal caffeine intakes greater than 70 to 300 mg/day and low birthweight *(Caan and Goldhaber 1989, Martin and Bracken 1987, Fenster et al. 1991a,b, Vlajinac et al., 1997*). Dose-response relationships have been noted in the two studies mentioned first.

A meta-analysis *(Fernandes et al., 1998)* including three of these and four other studies (*the studies are: Caan and Goldhaber 1989, Fenster et al. 1991a,b, Fortier et al. 1993, Linn et al. 1982, Martin and Bracken 1987, McDonald et al. 1992, Mills et al. 1993)* with extractable data showed an overall risk ration of 1.51 (95 % CI 1.39-1.63) for low birthweight (< 2500 g) in 64,268 pregnancies of women consuming > 150 mg caffeine per day. However, although the odds ratios in the individual studies were adjusted for some confounding factors, the meta-analysis used unadjusted data only. Adjustment of individual studies for confounding factors significantly would decreased the odds ratios for low birth weight calculated in these studies.

There are several other studies, which showed only a very weak decrease in birthweight after high consumption of caffeine (4 cups and more/day) (*Olsen et al., 1991)* or no association at all (*Fortier et al., 1993, Shu et al., 1995, Santos et al., 1998, Grosso et al., 2001).*

The study by *Grosso et al. (2001)*, for example, is one of the methodically better studies taking into account several potential confounders and distinguishing between exposures during the first and third trimesters, but only 2% of the participating women consumed more than 300 mg caffeine per day during month 7 of the pregnancy. The authors reported an adjusted odds ratio of 1.0 with a wide 95% confidence interval (0.37-2.70) for > 300 mg/day during month 7.

A recent study by Clausson et al., 2002 with relatively good assessment of exposure and confounding factors does not support an association between moderate caffeine consumption and reduced birth weight, gestational age, or fetal growth.

Klebanoff et al., 2002 found an association between an increasing risk of reduced fetal growth only among women who smoked. However, since paraxanthine concentrations could not be related to an amount of caffeine consumption the results cannot be used for a quantitative assessment.

Based on the current data, it is not possible to decide whether

a) the observed associations between caffeine consumption and low birthweight are due to (residual) confounding or recall bias, since in almost all studies data on the wide range of even the known confounders were insufficient and exposure to caffeine has been determined retrospectively by interviews/questionnaires/ or
b) true associations have been masked in the negative studies by non-differential misclassification of caffeine exposure or have been missed due to a lack of power.

It might be suggested that caffeine intake up to 3-4 cups/day or 300 mg caffeine/day is unlikely to cause a relevant reduction in birthweight.

However, it cannot be excluded that higher caffeine consumption (>300 mg/day) exerts a small, but measurable effect on fetal growth.

3.1.1.5.3 Prematurity and abortion

Prematurity

Information concerning prematurity was insufficie nt for conclusions to be drawn about an effect of coffee consumption by *IARC, 1991,* whereas caffeine consumption over a range of moderate to high intakes has been reported to increase the risk of prematurity in a recent study *(Wisborg et al., 1996).*

Spontaneous abortion

A meta-analysis *(Fernandes et al., 1998)* including six studies *(the studies are: Armstrong et al. 1992, Dominguez-Rojas et al. 1994, Fenster et al. 1991a,b, Infante-Rivard et al. 1993, Mills et al. 1993, Srisuphan and Bracken 1986)* with extractable data showed an overall risk ratio of 1.36 (95 % CI 1.29-1.45) for spontaneous abortion in 42,988 pregnancies of women consuming > 150 mg caffeine per day. However, although the odds ratios in the individual studies were adjusted for some confounding factors, the meta-analysis used unadjusted data only. Adjustment of individual studies for confounding factors significantly decreased the odds ratios for spontaneous abortion calculated in these studies.

A potentially important factor which has not been addressed in this meta-analysis is the change in caffeine consumption due to pregnancy-related nausea. Nausea can be considered as a marker for a healthy pregnancy (*Stein and Susser 1991*).

Since nauseated women consume less caffeine and have a reduced risk of spontaneous abortion, incomplete data on nausea and vomiting could lead to an overestimation of the risk associated with high levels of caffeine consumption.

Cnattingius et al. (2000) point out that results of epidemiologic studies have given inconclusive results on the association between caffeine consumption and spontaneous abortion. This might at least partly due to the fact that most studies have not included data on symptoms of pregnancy (*Armstrong et al., 1992, Dlugosz et al., 1996, Infante-Rivard et al. 1993, Mills et al. 1993, Parazzini et al., 1998, Srisuphan and Bracken, 1986*) while those that did have used fairly insensitive markers such as presence or absence of nausea at any time during pregnancy (*Fenster et al.1991a,b, Fenster et al., 1997, Klebanoff et al., 1999, Kline et al., 1991).*

According to *Cnattingius et al. (2000)* only one study with sufficient sample size focused on the first trimester of pregnancy when changes in caffeine intake, pregnancy-related symptoms, and the majority of spontaneous abortions occur.

Cnattingius et al. (2000) found an association between caffeine consumption and spontaneous abortion only in non-smokers (doses, odds ratios, and 95% confidence intervals as follows: 100-299 mg/day: 1.3 (0.9-1.8), 300-499 mg/day: 1.4 (0.9-2.0), >= 500 mg/day: 2.2 (1.3-3.8). However, retrospective exposure assessment based on interviews by midwives is a limitation of this study, and spurious positive results due to increased caffeine ingestion among the case patients in response to lessening of the severity of symptoms cannot be ruled out.

Klebanoff et al. (1999) reported an association of serum paraxanthine, a caffeine metabolite, with an increased risk of spontaneous abortion only at very high concentrations (>= 95th percentile). In this study most of the case women had spontaneous abortions in the second trimester, and the use of paraxanthine as a marker of caffeine dose has to be regarded with caution (intra- and interindividual variations in caffeine metabolism, short half-life, long-term storage).

A recent study by *Wen et al.* (2001) showed no association between caffeine consumption and spontaneous abortion in women who did not report nausea. However, the authors did observe an association between caffeine consumption of 300 mg/day and more and spontaneous abortion in women reporting nausea (odds ratio 5.4, 95% confidence interval 2.0-14.6). This is based on 4 cases only, prospective data on caffeine intake and nausea status and duration have been collected only monthly, and nausea severity has not been taken into account. Thus, other explanations than a causal relationship with caffeine consumption have to be considered.

In conclusion, caffeine intake up to 3-4 cups/day or 300 mg caffeine/day is unlikely to be causally related to spontaneous abortions. Nevertheless, in some subgroups of women (e.g. non-smokers, women with nausea), higher caffeine consumption (>300 mg/day) might increase the risk of spontaneous abortions.

3.1.1.5.4 Congenital anomalies

Based on two cohort and four case-control studies it was concluded, that taken together these studies do not provide evidence of a teratogenic risk of coffee intake *(IARC, 1991)*. Two studies in mothers taking caffeine-containing drugs during pregnancy showed either a nonsignificant increase of congenital malformations in cases (2.4 %) compared to controls (1.5 %) *(Nelson and Forfar, 1971)* or a slight nonsignificant decrease (RR=0.98, 95 % CI 0.7 to 1.2) *(Heinonen, 1982)*. More recent studies showed no relationship between caffeine consumption during pregnancy and incidence of malformations in offspring *(Olsen, 1991, Olsen et al., 1991)*. Retrospective information on caffeine intake during pregnancy showed developmental delay or central nervous system dysfunction and congenital anomalies with coffee consumption of 2 or more cups of coffee *(Tanaka et al., 1990)*. In conclusion there is no relationship between caffeine consumption up to 2 cups/day and malformations.

3.1.1.5.5 Fetal effects

Fetal heart rate changes and increases in aortic peal velocities were observed in mothers after orally ingestion of a caffeine citrate solution (100 mg/m^2 body furface area) between 25 and 36 week of gestation *(Miller et al., 1994)*. In fetuses of mothers not exceeding a daily caffeine intake of 200 mg temporal distributions of fetal behavioural states resembled those found in most normal thrid-trimester pregnancies *(Devoe et al., 1993)*.

3.1.1.5.6 Effects in infants

Newborn cardiac arrhythmias was associated with maternal caffeine intake *(Hadeed et al., 1990, 1993)*. Maternal caffeine consumption was associated with central and obstructive apnea in infants *(Bancalari et al., 1991, Ford et al., 1998)*. Except breech presentation no infant outcome measures were associated with prenatal caffeine exposure in infants *(Barr et al., 1991)*.
Conclusion: Data are inadequate for an assessment.

3.1.1.5.7 Effects on sperms

The addition of caffeine to human sperm increased sperm motility *(IARC 1991)*. In a cross-sectional study in male volunteers aged 19-35 common life style factors (smoking, caffeine, and alcohol) were associated with increased frequencies of sperm aneuploidy (*Robbins et al. 1997)*. No significant effects of smoking, caffeine intake, and alcohol consumption on sperm morphometric parameters were observed in another cross-sectional study in male volunteers aged 18-35 *(Vine et al. 1997)*. Conclusion: Data are inadequate for an assessment.

3.1.2 Acute Toxicity

After oral application the LD50 for rats (10 animals/group/sex) was found to be 261-383 mg/kg bw; as clinical symptoms of toxicity, dyspnoea and staggering were seen after oral intake (BASF AG 1985a). In further reports the oral LD50 for rats was reported to be 200-400 mg/kg bw (NTP 1982a) and for mice 185 mg/kg bw (NTP 1982b). The inhalation of the substance by rats as an aerosol for a period of 4 h resulted in an LC50-value of ca. 4.94 mg/l. Irregular and accelerated respiration were noted in this study (BASF AG 1989b).
The LD50 for dermal application was >2000 mg/kg bw; no clinical symptoms of toxicity were observed (BASF AG 1988d)

Conclusion: In animals studies caffeine showed moderate toxicity after oral uptake and inhalation and a low acute toxicity after dermal treatment.

3.1.3 Corrosiveness and Irritation

The undiluted substance was not irritating to the eyes of rabbits. Mean irritation indices were 0.9 (corneal opacity), 0 (iritis), 1.6 (conjunctival erythema) and 0.6 (conjunctival edema). The strongest signs of irritation were observed in 3/3 animals within the first 24h. By day 8 only one animal showed slight corneal opacity and conjunctival redness. The substance in a 50% aqueous dilution was not irritating to the skin of rabbits (Irritation index was 0) (OECD guideline 404 and 405, BASF, 1985b).

Conclusion: Caffeine is not irritating to skin and eyes.

3.1.4 Sensitization

No valid data available.

3.1.5 Repeated Dose Toxicity

In a 90-day oral toxicity study, the test substance was administered in drinking water to groups of Fischer 344 rats and B6C3F1 mice (groups of 12 animals/sex).

Rats were given 188, 375, 750, 1500, and 3000 ppm in the drinking water (ca. 19.7, 42, 85.4, 151, 272 mg/kg bw/d for males and 23, 51, 104, 174, and 287 mg/kg bw/d for females, calculated from weight and water consumption); control groups were given tap water.

The body weight gains of all treated groups were decreased. The effect was significant in the highest dose only (reduction of 26%, males, 20%, females). Water consumption was decreased in rats given 3000 ppm, whereas it was increased in the 750 and 375 ppm groups. No marked changes in clinical signs of toxicity were observed up to 1500 ppm. No dose-related changes inclinical chemistry were seen. With one exception (cellular enlargement in salivary gland), no pronounced significant changes in gross morphology or microscopic findings were observed. The authors gave no description of adverse effects. The effect observed in the salivary gland was described as dose dependent in rats; in mice it was observed only in the highest dose group. The effects in the salivary gland were considered adaptive. Reversible effects in the salivary glands are a well known pharmacological effect of caffeine (sympathicomimetic). These morphological changes are not considered to be an adverse effect of the substance. Finally, microscopic evaluation of sex organs revealed no significant differences between exposed and control rats (NTP Expt., 1983).

NOAEL rat : 1500 ppm (male 151 mg/kg bw/d; female 174 mg/kg bw/d)

Mice were given 94, 188, 375, 750, and 1500 ppm in the drinking water (ca. 21, 44, 85, 130, 167 mg/kg bw/d for males; 25, 47, 88, 134, 180 mg/kg bw/d for females, caclulated from weight and water consumption); control groups were given tap water.

Mean body weight gain was significantly, but not dose-dependently depressed for the 188, 375, and 750 ppm male dose group animals by 26%, 25%, 18% resp., but not in the 1500 ppm dose. Females showed little variation in weight gain. Food consumption was unaffected. Water consumption was decreased by 10% and more in the 1500 and 750 ppm dose group animals, whereas the water consumption was increased by 10% and more in the 94, 188, 375 ppm dose group animals. Adaptive changes in the salivary glands were also observed in mice in the highest dose group only (explanation see rats). Additionally, no tumors were seen in the salivary glands of mice which were treated with caffeine in the drinking water over 2 years (Mohr et al. 1984). Since no clinical signs of toxicity, or changes in clinical chemistry were seen, neither were statistically significant changes in gross morpology or microscopic findings (including the sex organs) observed (NTP Expt., 1983), the highest dose was the NOAEL.

NOAEL mice : 1500 ppm (male 167 mg/kg bw/d; female 179 mg/kg bw/d)

Additionally no significant toxic effects were reported in older studies (i.p., drinking water or dermal application) that are poorly documented.

Conclusion:

In adequately performed studies, administration of high doses of caffeine (ca. 160 mg/kg bw in rats, ca. 170 mg/kg bw in mice) caused no significant toxic effects. In these studies no histopathological changes were found in the gonads of rats and mice. The findings of testicular athrophy and decreased absolute testis weights described in earlier feeding studies with Holtzman and Spraque Dawley rats could thus not be confirmed (Friedman et al., 1979, Gans 1984).

3.1.6 Genetic Toxicity

There were many studies for different endpoints available. All studies were evaluated and in the following text only the most relevant, well-documented studies are discussed.

Genetic Toxicology in vitro

Gene mutation in vitro

In a round-robin-study performed at several institutions the substance was negative in bacterial tests (Salmonella typhimurium TA98, 100, 1535, 1537, 1538 and E. coli WP2 uvrA) with and without metabolic activation tested up to 3333 ug/plate or 10, 000 ug/plate (Dunkel et al., 1985, Mortelmans et al., 1985,) and in the Mouse Lymphoma test up to 10620 ug/ml without metabolic activation (Amacher et al., 1980).

Generally, the tests for detecting gene mutations (e.g. bacterial tests, Ames tests, Mouse lymphoma test and HPRT tests (in diffentent cell lines) showed negative results. A poorly documented UDS test in human lymphocytes (tested up to 583 ug/ml) was also negative.

Chromosomal aberrations in vitro

Caffeine was not clastogenic in cytogenetic studies performed with human lymphocytes (tested up to 100 ug/ml exposure time 8h, which showed cytotoxic effects) (Aeschbacher et al., 1985), while test with CHL cell lines without metabolic activation (Ishidate, jr. 1977) showed a positive response, due in part to testing in concentrations above the levels recommended in the OECD/EU guidelines (i.e. over the 10mM level). In a poorly documented study, positive findings were also noted in CHO cells in concentrations of 5.5 mM. Eight in vitro SCE-assays performed with different cell lines gave negative (3), positive (4) and ambigous (1) results. The relevance, however, of results from SCE assays for the assessment of genetic toxicity is presently unclear.

Genetic Toxicology in vivo

Gene mutation

A single oral dose of up to 1000 mg/kg bw did not induce **UDS** in pancreatic cells from F344 rats treated with caffeine (abstract only, Steinmetz and Mirsalis, 1984).

Negative results were shown in a weakly documented **host-mediated assay** in mice with Salmonella typhimurium G46 tested with up to ca. 33 mg/kg bw, i.m. application (Gabridge and Legator, 1969). In a modified host-mediated assay in mice with E. coli K12, caffeine was also negative (2x91 mg/kg ip. injection) (King et al., 1979).

Chromosomal aberrations

The substance did not induce **chromosomal aberrations** in the blood of rats after administration in feed (46 mg/kg bw/d) for 117 weeks, (Granberg-Oehman et al., 1980) or in the testicular tissue of mice after a single i.p. administration of 200 mg/kg bw (Adler, 1966).

No chromosomal aberrations or aneuploidy was observed in the oocytes of mice after i.p. application of 150 mg/kg bw (Mailhes et al. 1996).

Investigations with lymphocytes from human volunteers who had a daily intake of 800 mg (4x200 mg) of caffeine over 4 weeks showed no increase in chromosome damage. The highest level of caffeine detected

in the plasma was 30 µg/ml. Isolated lymphocytes from untreated donors administered this concentration (30 µg/ml) several times were also negative. However, caffeine produced damage in human lymphocytes in culture after a single 48h treatment with 250-750 µg/ml (Weinstein et al. 1972).

Further cytogenetic tests with bone marrow cells from mice and rats gave no indication of a clastogenic effect (see IUCLID).

Most of the in vivo SCE-assays with rats, mice and hamsters were positive. However, in the 117 week feed study in rats (Granberg-Oehman et al., 1978) no SCE induction was observed. However, a toxicological relevance is questionable due to the other negative in vivo studies.

Caffeine was negative in the mouse bone marrow **micronucleus test** (i.p. administration of up to ca. 97 mg/kg) (King et al., 1979). In further micronucleus tests, Swiss CD-1 mice (in- and outbred mice) received 50, 75 or 100 mg/kg bw caffeine and Chinese hamsters received 75, 150 or 300 mg/kg bw by gavage twice with a 24h interval, and with the second dose being given 6h prior to sacrifice, or alternativly given once 30h prior to sacrifice. Only the highest dose (in the range of the LD50) caused an induction of micronuclei in hamsters and mice (Aeschbacher et al., 1986). Other poorly documented micronucleus tests with rats and mice have been published and were also negative.

A study was performed by i.p. application to compare the ability of caffeine to induce **micronuclei** (in mice and Chinese hamster) versus **chromosomal aberrations**, and **SCE** (in Chinese hamster) (Tsuchimoto and Matter, 1979). In the micronucleus test with mice the doses used were 100 and 250 mg/kg bw and they were administered via i.p. twice with an interval of 24h. In the studies with hamsters, 100 and 200 mg/kg bw were used. For the micronucleus screening and chromosomal aberration tests, the test substance was given twice via i.p. with an interval of 24h, and was only given one time via i.p. for the SCE test. Niether a clastogenic effect nor an increase in SCE was seen in any of the studies.

In a **Dominant lethal test** male mice were gavaged with caffeine at 90 mg/kg bw for 5 consecutive days or received it via drinking water at levels of 112 mg/kg bw for 8 weeks. No mutagenic induction of dominant lethals, preimplantation losses or depression of female fertility attributable to the test substance was observed (Aeschbacher et al., 1978). All other dominant lethal studies were likewise negative.

Conclusion:
A large number of in vitro results are available and were summarized in a comprehensive review (IARC No. 51): Salmonella and classic E. coli studies were mostly negative. Special E. coli strains and Saccharomyces showed positive results. In terms of gene mutation in mammalian cell cultures and UDS assays, the results were consistently negative. Only at high concentrations were some indications of clastogenic activity in cell lines found.

In the majority of in vivo tests (MNT; CA, DL, HMA) negative results were obtained in terms of mutagenicity and clastogenicity. On the whole, the conclusion is drawn that under exposure relevant conditions there are no indications of genotoxicity of caffeine. This is also the overall assessment of the IARC evaluation (see publication No. 51, 1991 for more details).

3.1.7 Carcinogenicity

In a 104 week drinking water study, the substance was administered to Sprague-Dawley rats (groups of 50 animals/sex) at concentrations of 200, 430, 930 and 2000 ppm (12, 26, 49, 102 mg/kg bw/d males and 15, 37, 80, 170 mg/kg bw/d, females). There was a slightly increased mortality in males at 2000 ppm. Decreased body weights were found in both sexes at 930 ppm (11%) and 2000 ppm (25%), associated with reduced food and water consumption.

There were no statistically significant differences between control and treated animals for tumor incidences of any type except for mammary fibroadenomas. The incidence of mammary fibroadenomas showed a significant inverse dose-response relationship (26% high dose vs. 50% control) (Mohr et al. 1984).

Several other carcinogenicity studies, including initiation-promotion studies, have been performed, and all of them were negative; however, they were judged by IARC to be of limited value (e.g. only one dose was used, or only one sex, or only one tissue (mammary gland of mice), or the animals were not exposed to the test substance for 2 years). Due to these limitations they were not used as key studies for caffeine.

Conclusion:

There was no statistically significant increase in the tumor incidence of caffeine treated rats as compared to controls, even at doses exceeding the maximum tolerated dose and given to animals over a major portion of their lifespan.

3.1.8 Toxicity to reproduction

Rat Study

The potential reproductive toxicity of caffeine in Sprague-Dawley rats was evaluated using the Reproductive Assessment by Continuous Breeding (RACB) protocol.

Task 1 (dose-finding study)

Caffeine at dose levels of 0, 50, 100, 150 and 200 mg/kg was given via gavage to 8 animals/sex/dose for 28 consecutive days. Based on decreased body weights, food consumption, increased water consumption, and mortality the dose levels for the continuous breeding phase were set at 12.5, 25, and 50 mg/kg bw/d (5 ml/kg).

Task 2 (cohabitation period)

Male and female Sprague-Dawley rats (20 pairs/group) were exposed to caffeine in deionized water by gavage. During 16 weeks of cohabitation, live pup weight adjusted for litter size was decreased by 7, 7, and 8% in the 12.5, 25, and 50 mg/kg bw/d dose groups, respectively. No differences were observed in litters per pair, number of live pups per litter, proportion of pups born alive and sex ratio.

Decreased pup weight was observed concomitant with dose-dependent reduced dam weight gain. At necropsy, no differences were noted in F0 male or female absolute organ weight data; however, many relative organ weights were increased in all dosed groups when compared to controls. These differences were attributed to the decrease in terminal body weights. No treatment-related gross or microscopic lesions were observed in kidneys, testes or epididymis of F0 males. In the F0 generation sperm parameters (velocity and average radius) were decreased (7-12% and 22-36% resp.) in all treated males. Sperm motility was dose-dependently decreased (3%) and percent normal sperm was slightly decreased in the high dose males.

Task 3 (crossover mating)

A crossover mating trial revealed no changes on male or female fertility or in pup weight. Reproductive parameters (as describe in Task 2) were comparable between dose groups when naive males were mated with control or 50 mg/kg bw/d females and when naive females were mated with control or 50 mg/kg bw/d males.

Task 4 (second generation evaluation):
No mortality was observed in any of the F1 animals. No treatment-related differences were observed in pup weights during lactation (post natal day 1-21). From the initiation of dosing (post natal day 22) through the maturation phase up to the termination of Task 4, mean body weights of the F1 low-to-high dose males and females were decreased dose-dependently (approximately 12%,18% and 23% when compared to controls). Mean body weight and feed consumption were decreased (5-19%) in all treated groups.

A decrease in the number of live F2 pups per litter (21%) and the proportion of pups born alive (4%) in the 50 mg/kg bw/d dose group was noted. No differences in other endpoints were observed between dosed groups and controls.

At necropsy, many decreases were noted in F1 absolute organ weights and
many increases in F1 relative organ weights were observed in all treated groups. These differences may be attributed to the decreased terminal body weights. No treatment-related gross or microscopic lesions were observed in the F1 animals.
The motility and velocity of sperms was slightly decreased (4% and 9% resp.) in the 50 mg/kg F1 males and average radius was decreased (23-26%) in the males of mid- and high dose group. The remaining sperm parameters were unaffected.

A no-observable-adverse-effect level (NOAEL) was not established in this study as the 12.5 mg/kg animals displayed reduced body weight gain in F0 and F1 animals (NTP, 1996).

Mice studies
Caffeine was tested for its effects on reproduction and fertility in Swiss CD-1 mice at two laboratories, each using a variation on the standard RACB study design. One laboratory performed Tasks 1, 2, and 3, while the other laboratory performed Tasks 1, 2, and 4 (see below) (NTP 1984 a,b).

In the first study:
Task 1 (dose-finding study)
Caffeine was administered via drinking water at dose levels of 0, 10, 30, 100, 300 and 1000 ppm (ca. 2, 6, 20, 60 and 200 mg/kg) to 8 animals/sex/group for 14 days.
All 16 animals exposed to 1000 ppm died within 2 weeks. The cause of the dead was diagnosed as cardiac myodegeneration and tubular nephrosis. Data on body weight, clinical signs, and food and water consumption were collected during this dose-range-finding phase, and used to set exposure concentrations for Task 2 at 0, 120, 250, and 500 ppm (= ca. 22, 44, and 88 mg/kg bw/d) in drinking water.

Task 2 (cohabitation period)
In this phase 40 animals/sex for the control and 20 animals/sex for the treated groups were paired.
The animals were exposed to caffeine via drinking water during a 7 day premating period and during the 100 day cohabitation period.
Water consumption and body weights were not affected. Three control mice, 1 low dose, and 1 middle dose mouse died during the study (no data were given about the cause). Treated mice were also reported to have lost facial hair, but the percentages and groups involved were not specified.

There was no effect on the mean number of litters/pair or on the mean number of pups/litter. However, there was a 20% reduction in the number of live male pups/litter in the 500 ppm group. The proportion of pups born alive was reduced by 3%, 5%, and 5% in the low, middle and high dose groups, respectively. Additionally, pup body weight adjusted for litter size was reduced by 4% at the high dose.

Task 3 (crossover mating)
A crossover mating trial was performed. There were no differences between the groups in the mating and fertility indices, and no differences with respect to pup number or viability or weight.

Task 4 was not performed in this study. After 7 days of vaginal smears to evaluate cyclicity, the control and high dose (500 ppm) Task 2 mice were killed and necropsied. Female body weight was reduced by 5%, while relative organ weights were unchanged. Ante-mortem vaginal cyclicity was unaffected. Male body weight was unchanged by consumption of 500 ppm caffeine but adjusted liver weight was increased by 10%. Absolute testis weight dropped by 7% and adjusted seminal vesicles weight decreased by 12%. Sperm motility values for controls was low (47% motile), so the 21% reduction in the treated group should be viewed with caution. Similarly, the control epididymal sperm density was nearly equal to half of the subsequent control values for this lab, so the significant increase in sperm density in the caffeine-treated group is likely erroneous.

In conclusion, the slight but significant reductions in (male) pup number, pup viability, and adjusted pup weight suggest that caffeine produced some slight reproductive toxicity. This occured in the presence of slight indications of general toxicity (body or organ weight changes) (NTP 1984 a).

NOAEL (mouse): ca. 22 mg/kg bw/d (120 ppm) (F0 parental) (Task 2)
22 mg/kg bw/d (120 ppm) (F1 offspring) (Task 2)

Caffeine was tested in the other laboratory that performed Tasks 1, 2, and 4.

Task 1 (the dose-range-finding)
8 male and 8 female CD-1 mice per dose group were given 0, 12, 33, 100, 300 and 1000 ppm (ca. 2.4, 6.6, 20, 60, 200 mg/kg) caffeine in their drinking water for 14 days. Based on body weights, clinical findings, food and water consumption, the concentrations for Task 2 were set at to be 0, 120, 250, and 500 ppm (= 22, 44, and 88 mg/kg/d).

Task 2 (cohabitation period)
In this phase 40 animals/sex for the control and 20 animals/sex for the treated groups were paired.
The caffeine treatment was during the 7 day premating period, the 98 day cohabitation period and the 21 day segregation period. Water consumption was not affected in all treated groups. For the F0 animals, there were no effects on body weight. Alopecia occurred in 55% of the mid dose and 50% of the high dose animals.

While there were no exposure-related changes in the number of litters/pair, viability, or adjusted pup weight, the number of live pups per litter, averaged over 4-5 litters was decreased for the mid (15%) and high dose (20%) animals.

Task 4 (second generation evaluation)
The offspring from the last litter of control and high dose (500 ppm) mice were reared by their dams until weaning, and then they were given the same treatment as their parents until mating at 74 ± 10 days of age. In the second generation mating trial, there were no changes in any reproductive endpoint.
At necropsy, in the 500 ppm group, male body weight was reduced by 8% while male adjusted liver weight increased by 8%. No change was found in female body organ weights, or in any sperm endpoint.

In summary, a reduction in the number of live pups/litter for the F0 generation was the only reproductive effect observed in this study. This occurred in the absence of a change in body weights in the F0 parental mice, but in the presence of clinical findings in form of alopecia (NTP 1984 b).

NOAEL (mouse): ca. 22 mg/kg bw/d (120 ppm) (F0 parental) (Task 2)
22 mg/kg bw/d (120 ppm) (F1 offspring) (Task 2)

NOAEL (mouse): ca. 88 mg/kg bw/d (500 ppm) (F1 parental) (Task 4)
88 mg/kg bw/d (500 ppm) (F2 offspring) (Task 4)

In addition to the key studies described above, there are numerous other studies some of them with unusual study designs described in the IUCLID master. In a two generation study with Wistar rats the administration of 30 mg of caffeine/kg bw led to a marked degeneration of the testis in the F0 generation males after 38 treatment days. The findings were characterized by a significant overall size reduction in the testis, breakdown of the germinal epithelium, accumulation of cellular debris in the lumen of seminiferous tubules, and a significant reduction in the abundance of mature spermatozoa (Pollard et al. 1988).
In another study when caffeine was administered to the dams during pregnancy (30 mg/kg/day from day 1 of gestation until sacrifice), a significant inhibition in the differentiation of the interstitial tissues and Leydig cells was observed in their male fetuses. In the ovaries of female fetuses caffeine had no influence on the mitotic rate or morphology of germ cells. Later in development the numbers of female germ cells entering meiosis were comparable to the controls (Pollard et al. 1990).
In a further 2-generation study in Sprague-Dawley rats with an unusual study design, it was demonstrated that the exposure to caffeine (30 and 60 mg/kg/day) did not affect the sexual receptivity, fertility, gestation length, or maternal behaviour of the F1 females, but parturition was prolonged and the viability of the F2 generation was seriously jeopardised (Pollard, et al. 1992). All three studies are not comparable with guideline-studies, and thus, these data are difficult to assess.

Three experiments were conducted to investigate the effects of feeding caffeine to Osborn-Mendel and Holtzmann rats at a dietary level of 0.5% (ca. 230 mg/kg/d). An induction of testicular atrophy, oligospermatogenesis and aspermatogenesis was observed after 14, 64 and 75 weeks in Osborn-Mendel rats and after 19 weeks in Holtzmann rats (Friedman at al. 1979, Weinberger et al. 1978). Because of the high mortality (75% at 14 weeks, 35% at 64 weeks, 60% at 75 weeks, 63% at 19 weeks) and the single dose tested, the studies are regarded to be of limited value for assessing the toxicological potential of the substance. Similar findings were obtained in a study with Sprague Dawlay rats, which were fed 0.5% caffeine (Gans, 1984). However, no data were given about the group size, surviving animals and the number of rats with testicular atrophy.
In contrast, testicular findings were not observed histopathologically in well documented subchronic studies in rats and mice (see 3.1.5).
Conclusion:
In summary in several well documented studies, caffeine resulted in slight reproductive effects at high doses (e.g. reduced number of pups born alive per litter) occurring in the presence of general toxicity (body weight gain) in parental rats and mice.
In well documented 90 day-studies performed in rats and mice, no significant differences in sperm morphology, vaginal cytology and histopathology of the gonads were seen (see 3.1.5.).

3.1.9 Developmental Toxicity / Teratogenicity

Developmental effects were studied in female Osborne-Mendel rats treated on days 0 to 20 of gestation. The substance was administered in the drinking water at concentrations of 70, 180, 360, 700, 1000, 1500, and 2000 ppm. The corresponding daily caffeine intake were ca. 10, 27, 51, 87, 116, 160, and 205 mg/kg bw/d. Sacrifice of the dams and examination of the pups was made on day 20 of gestation. Decreased maternal food and water consumption and significantly decreased maternal body weight gain [by 8% (700 ppm), 25% (1000 ppm), 50% (1500 ppm) and 71% (2000 ppm)] were observed. At 1500 and 2000 ppm, decreased implantation efficiency, increased resorptions, and decreased mean number of viable fetuses were noted. The number of runts was increased at 1000 ppm and higher. Decreased fetal weight and length, and an increased incidence of edematous fetuses were observed at 700 ppm and higher. Variations in the form of sternebral ossification deficiencies were increased at all dose levels except at 70 ppm, and in the form of skeletal ossification deficiencies in a dose-related manner from 700 ppm and higher. No teratogenic effect was found (Collins et al., 1983).

NOAEL	maternal toxicity:	360 ppm (ca. 51 mg/kg bw/d)
	fetotoxicity :	70 ppm (ca. 10 mg/kg bw/d)
	teratogenicity :	2000 ppm (> 205 mg/kg bw/d)

Similar results were obtained in a drinking water and a gavage study with Osborn-Mendel rats (Collins et al. 1981 and 1987). In the drinking water study body weight depressions as well as skeletal retardations in fetuses were observed in doses of 360 ppm and higher. In the gavage study a teratogenic effect was found in higher maternally toxic doses (80 mg/kg bw and higher).

In two NTP studies, CD rats were administered the test substance by gavage.

Administration of 0, 40, and 80 mg/kg bw/d on gestation days 1 to 19 to groups of 20 rats (developmental evaluation on gestation day 20) resulted in maternal toxicity indicated by signficantly reduced maternal weight gain in all treated groups (35% and 43% resp.). Fetal weight was significant reduced (13%) at the high dose level. The number of implantation sites, the percent of live fetuses/litter and the number of resorption and dead fetuses were not affected. No increase in the rate of external, visceral, or skeletal malformations was seen (NTP, 1984c).

LOAEL: 40 mg/kg bw/d (maternal toxicity)

NOAEL: = 40 mg/kg bw/d (fetotoxicity)

NOAEL: = 80 mg/kg bw/d (teratogenicity)

In the second study groups of 12 dams were administered 0, 10, 20, and 40 mg/kg bw/d of the substance on gestation days 1 to 20 and were allowed to deliver. The pups were subsequently evaluated for postnatal growth and several functional parameters. No adverse effects on offspring physical development, behaviour or cardiovascular function were observed, although maternal body weight gain was significantly reduced in all treated rats (14%, 12% and 18% resp.) (NTP, 1984c).

LOAEL: 10 mg/kg bw/d (maternal toxicity)

NOAEL: = 40 mg/kg bw/d (fetotoxicity)

NOAEL: = 40 mg/kg bw/d (teratogenicity)

Several studies were performed to assess reproductive and/or developmental toxicity with brewed or instant coffee. In these studies the animals received coffee as their drinking fluid, which yielded doses of

caffeine of ca. 38-80 mg/kg. In all studies with the exception of one (see below), no teratogenic effects were found. In some cases delayed ossification of the sternebrae was observed. In more recent guideline-like studies where rats were treated with higher doses of caffeine, these findings (malformations) could not be confirmed (see below).

In this older study with rats, malformations were observed. Namely, in a combined subchronic, reproductive, developmental study with freshly percolated coffee in drinking water (9, 19, 39 mg/kg bw/d) or when caffeine was administered by gavage or in drinking water (30 mg/kg bw/d), cleft palates and delayed ossifications were observed, however these findings were not dose-dependent. For coffee intake of 0%, 12.5%, 25% and 50% the number of observed fetuses with cleft palates were 1/423; 8/207; 5/225; 4/229, and for caffeine gavage intake 1/252, and caffeine in drinking water 2/245, only. Delayed ossification was found after coffee intake in 0/256; 8/128; 62/141; 11/148 and after caffeine intake in 12/171 and 15/160 animals respectively. The animals received coffee or caffeine before mating, throughout gestation and up to 27 days after parturition. Effects on fertility, litter size and neonatal growth were not observed. No information about maternal toxicity was given in the report (Palm et al., 1978). The fact that these results were not dose-dependent calls into question their relevance. In several studies performed in mice caffeine was given either once by i.p. injection, by feed (in pellets) or via drinking water. Cleft palats were observed in the i.p. and feeding study, but not in the drinking water study. It is worth noting that feed and water study were parallel studies using the same dose. It is known from literature (Schwetz et al.1977, Beyer and Chernoff, 1986) that in this species stress (caffeine is a sympathomometic), or a decrease in water intake during gestation may induce this type of malformation. Therefore, no mouse study was chosen as a key study.

A behavioral study was performed with forty adult monkeys which were administered caffeine in drinking water at concentrations of 0.15 and 0.35 mg/ml (ca. 10-15 and 25-30 mg/kg bw/d) before, during and after pregnancy.
Previously reported results indicated that exposure to caffeine resulted in a dose-related increase in reproductive failure (stillbirths, miscarriages) and decreased maternal weight gain and decreased infant birth weight. These results may be the consequence of elevated serum levels of not only caffeine but also its pharmacologically active metabolite theophylline, which is the major metabolite in monkey but not in human.
Analysis of blood and 24-hour urine samples (collected every 2 weeks) revealed a number of both pregnancy and treatment-related effects: decreased levels of serum cholesterol and triglyceride during pregnancy in all groups (pregnancy-related), increased levels of serum and urine creatinine in the treated groups (substance-related), unaltered serum glucose levels in the high dose group (substance-related, this value usually declines during pregnancy), and depressed levels of serum estrogen in the high dose group (substance-related).
According to the authors, these findings indicated that the test substance may influence maternal physiology during gestation in the monkey.
Additionally, the somatic development (like body weight, tooth eruption, skelettal development and measures etc.) of the infants was monitored. Maternal blood and milk concentrations of the test substance were similar to infant blood concentrations.
Infant body weights and somatic measurements (like bone and head lengths), were reduced over the first 30 days in males. The deficits were reversible and not evident after one year of age. Tooth eruption and milk consumption were not affected. According to the authors, this indicated that caffeine can alter infant somatic development (treated monkeys were significant smaller than controls) when consumed during pregnancy.
Behavioral tests were conducted in the infants. At 30 days of age, the infants were trained to press a button to receive a reward (infant formula). Thereafter, a variable number of button presses (variable ratio

schedule) were required to get formula. Monitoring of feeding time revealed that the treated infants spent significantly more time feeding than controls. On the variable ratio schedule, the high-dose group had consistently longer pause times and longer interresponses than controls. According to the authors, these results indicated that in utero exposure to caffeine and its metabolites resulted in altered behavioral patterns in infant monkeys (Gilbert and Rice, 1991a/b, 1994).

There were further developmental neurotoxicology studies, mostly performed in rats. However, according to IARC monograph Vol 51(1991), these studies were reviewed and the effects observed were not consistent across the studies. Thus, it was concluded by IARC that "caffeine may cause subtile changes in discrete neuronal subsystems but has not to be regarded to be a neurotoxicant in the sense of disrupting primary neuronal systems."

Conclusion:

In maternally nontoxic doses no teratogenic effect was observed in several studies with rats. Slight fetotoxicity was observed in the rat study in the absence of maternal toxicity.

In summary, animal studies demonstrate that high bolus-doses of caffeine can result in gross malformations and resorptions, while prolonged sipping or infusion of the same total dosage during organogenesis caused only reversible delays in growth. The consideration of pharmacokinetic data is essential for appropriate intra-species and interspecies risk extrapolation. Animal data indicate that the probable blood level of caffeine required to produce teratogenic effects is in excess of 60 µg/ml. This blood level can only be reached in rodents as short-term peak concentrations by administration of large bolus dosages (gavage) in amounts exceeding 40-60 mg/kg bw/d. It can also be assumed that this would correspond to 800 mg/kg bw/d of caffeine given to rats in the drinking water. Using this hypothetical data, an 800 mg/kg bw/d dosage of caffeine would require a 70 kg human to consume about 50 g of caffeine within a short time period. This cannot be achieved by consuming usual caffeine-containing drinks over several hours (both in human and animal) (Christian and Brent, 2001).
Christian and Brent (2001) concluded, that pregnant women, who do not smoke or drink alcohol and who consume moderate amounts of caffeine (<5-6 mg/kg bw/d spread throughout the day) do not have an increased risk of reproductive effects.

4 Hazards to the environment

4.1 Aquatic effects

The following acute toxicity test results with aquatic organisms are available:

Leuciscus idus	LC50(96h) 87 mg/l	BASF AG, 1988b
	NOEC (96h) 46 mg/l	
Daphnia magna	EC50(48h) 182 mg/l	BASF AG, 1989a
	EC0 (48h) 3.91	
Scenedesmus subspicatus (Desmodesmus subspicatus)	ErC50(72h) >100 mg/l	BASF AG, 2001b
	ErC10 (72h) > 100 mg/l	
Pseudomonas putida	EC50(17h) 3490 mg/l	BASF AG, 1988c

All effect values are related to nominal concentrations. In the alga test the test substance concentration was monitored by HPLC. The measured concentrations were between 96.5 and 105.8 % of the nominal values and the results were related to nominal concentrations.

Based on this data, caffeine is considered as harmful to aquatic organisms.

Results from prolonged or chronic studies are not available.

Based on the most sensitive data, Leuciscus idus LC50(96h) 87 mg/l, a PNEC for the aquatic compartment of 0.087 mg/l can be derived by applying an assessment factor of 1000, according to the Technical Guidance Document for the EU risk assessment procedure.

4.2 Terrestrial effects

In a non-standard study the effect of caffeine on rice seedlings was investigated over a 6 day period.
0.5 – 10 mM caffeine inhibited the growth dose-dependently. Shoot elongation was inhibited by 50 % with 2.5 mM caffeine (485 mg), whereas root elongation was inhibited by 80 % with one treatment at the same concentration (Smyth, 1992). As the tests were performed without soil but with filter paper, the results cannot be used for the derivation of a PNECsoil.

The LD50 for red flour beetle, exposed to flour medium treated with caffeine, was 288 mg/kg for adults and 251 mg/kg for larvae (Mondal et al., 1992).

Investigations with red-winged blackbirds and starlings showed LD50 values of 316 mg/kg BW and >500 mg/kg BW respectively (Schafer et al., 1983).

5 Conclusions and Recommendations

5.1 Conclusions

In 1999 the estimated world production amounts to 10,000 – 15,000 tons including 3,000 to 4,000 tons of natural caffeine. Worldwide, there are 18 production sites known for the technical product caffeine and about 7 to 8 for natural caffeine.
The substance is predominantly used in the food (80 %) and pharma sector (16 %). A smaller part is used in cosmetics (3 %) and in technical applications (1 %).
Releases into the environment may occur during production of caffeine, during formulation and use of food and pharmaceuticals.
Measured data on emission into the atmosphere or into surface water via waste water treatment plants are not available.
According to a Mackay I model the target compartment for the substance is the hydrosphere with 99.99 %.
Caffeine can be regarded as readily biodegradable. Hydrolysis is not expected to occur. In the atmosphere the substance will be photodegraded by reaction with hydroxyl radicals with an estimated half-life of 19.8 h. The substance has no potential for bio- or geoaccumulation.
Short-term tests are available for fish, daphnia and algae. Based on acute toxicity studies caffeine can be considered as harmful to aquatic organisms. Following the EU risk assessment procedure the PNEC for the aquatic compartment can be calculated to 0.087 mg/l by applying an assessment factor of 1000 on the most sensitive species (*Leuciscus idus* LC50(96h) 87 mg/l).

In animals studies caffeine showed moderate toxicity after oral uptake and inhalation and a low acute toxicity after dermal treatment.
LD50 rat oral: 261-383 mg/kg, LC50 rat inhalative: ca. 4.94 mg/l/4h; LD50 rat dermal: > 2000 mg/kg)
The undiluted substance was not irritating to the eyes of rabbits; the substance in a 50% aqueous dilution was not irritating to the skin of rabbits.

In a 90-day-drinking water study in rats and mice a slight decrease of body weight gain was observed. No clinical signs of toxicity or significant gross lesion were seen in either rats and mice. The NOAEL for rats was 1500 ppm (ca. 151 - 174 mg/kg bw/day) and for mice 1500 ppm (ca. 167-179 mg/kg bw/day).

There are numerous studies available concerning genetic toxicity in vitro and in vivo. Collectively the results indicate no evidence of mutagenic effects. The weakly positive result reported in one micronucleus study with mice has so far not been confirmed.

There was no statistically significant increase in the tumor incidence in treated animals as compared to controls even at doses exceeding the maximum tolerated dose and given to rats over a major portion of their lifespan.

Caffeine resulted in reproductive effects occurring in the presence of general toxicity in parental rats and mice. A NOAEL in rats was not established. NOAEL: mouse 22 mg/kg bw/d (F0 parental, F1 offspring), 88 mg/kg bw/d (F1 parental, F2 offspring).

No teratogenic effects were observed in several studies in rats. Fetotoxicity without maternal toxicity was observed in one study. NOAEL: 360 ppm (51 mg/kg bw/d) (maternal), 70 ppm (10 mg/kg bw/d) (fetotoxicity), 2000 ppm (205 mg/kg bw/d) (teratogenicity). However, in two other studies this finding was not confirmed. No NOAEL for maternal toxicity could be established; the NOAEL for developmental toxicity was 40 mg/kg bw/d; no teratogenic effects were observed.

Absorption from gastrointestinal tract is rapid. Peak plasma levels are reached after 15 to 120 minutes after ingestion. The elimination half-life in adults is about 2.5 to 4.5 hours. A small percentage is excreted in bile, salvia, semen and breast milk. In both humans and rats, excretion mainly occures via urine (about 90 % dose in rats; > 95 % in humans).
Caffeine metabolism is qualitatively relatively similar in animals and humans. The main metabolic pathways are: demethylation and hydroxylation of the 8-position leading to the formation of the respective uracil and uric acid derivatives. There are, however, some quantitative differences in the metabolic profile.

Low doses (up to 2 µg/ml in blood) stimulate the central nervous system, while high blood concentrations (10-30 µg/ml) produce restlessness, excitement, tremor, tinnitus, headache, and insomnia. Caffeine can induce alterations in mood and sleep patterns, increase diuresis and gastric secretions. Acute toxicity is rare and is the result of an overdose. Lethal dose is estimated to be 5 g.
Caffeine and coffee consumption are highly correlated in most populations studied; thus it is difficult to separate the two exposures in epidemiologic investigations. No association between moderate consumption of coffee/caffeine and cardiovascular diseases was demonstrated in more recent studies. In short-term clinical trials an increase in blood pressure was seen, whereas in other surveys no relationship between caffeine consumption and elevation of blood pressure was observed. Caffeine consumed in moderate amounts did not cause persistent increase in blood pressure in normotensive subjects. Effect on cardiac rhythm is still in debate. Small increase in calcium excretion associated with coffee/caffeine intake was seen in subjects with dietary calcium deficiency. Caffeine has weak reinforced properties, but with little or no evidence for upward dose adjustment, possibly because of the adverse effects of higher doses. Withdrawal symptoms, although relatively limited with respect to severity, do occur, and may contribute to maintenance of caffeine consumption. Caffeine use is not associated with incapacitation. There is little evidence for an association of caffeine intake and benign breast disease. No association was found in a study with biopsy-confirmed controls.
A cohort study with short follow-up period showed no association between caffeine consumption and mortality from cancers at all sites. Case control studies of breast cancer showed no association to caffeine intake. Available data are consistent with a weak association between bladder cancer and caffeine intake, but the possibility that this is due to bias or confounding cannot be excluded. Effect of coffee consumption on colon and pancreas is in debate.
There are conflicting reports on the effect of caffeine on human reproduction. A teratogenic effect has not been proven. While caffeine intake up to 3-4 cups/day or 300 mg caffeine/day is unlikely to be causally related to spontaneous abortions or relevant reduction of birth weight, an association between higher daily caffeine intake and these endpoints can not be excluded. Conflicting results exist regarding a potential relationship between caffeine/coffee consumption and delayed conception or infertility.

Risk characterization:

Caffeine is listed in GRAS Food Substances. The tolerance in foods is 0.02%. “The substance is generally recognized as safe when used in cola-type beverages in accordance with good manufacturing practice” (Code of Federal Regulations Title 21-Food and drugs revised as of April 1, 2001)
Caffeine in pharmaceutical use is described in specific regulation.

Workplace:
Taking worst case assumptions, the maximum exposure of workers during the filter changes is 1.2 mg/m^3. Considering this high exposure, which is unrealistical for 8 hours, the maximum uptake (absorption: 100 %; ventilation rate: 1.8 m^3/ h) is 17.28 mg/person (ca. 0.3 mg/kg bw/day).
With respect to the NOAEL in subchronic studies - NOAEL for rats was 1500 ppm (ca. 150 - 174 mg/kg bw/day) and for mice 1500 ppm (ca. 167-179 mg/kg bw/day) - there are safety factors of 500 an higher.
NOAELs for developmental toxicity, the most sensitive endpoint are: NOAEL: 360 ppm (51 mg/kg bw/d) (maternal toxicity), 70 ppm (10 mg/kg bw/d) (fetotoxicity), 2000 ppm (205 mg/kg bw/d) (teratogenicity). Even under this worst case assumption, there is still a safety factor of 33 for fetotoxicity. This safety factor is substantiated by a new publication of Christian and Brent, 2001 in which up to 5 –6 mg/kg caffeine uptake per day is regarded to have no reproductive risk for humans.

5.2 Recommendations

Environment: No recommendation for further work, as the substance is readily biodegradable, has a low bioaccumulation potential and is only moderately toxic to aquatic organisms.

Human Health: No recommendation for further work for the following reasons:

The pharmacological properties of caffeine are well known. There are many studies relevant to reproductive toxicity; some suggest an adverse effect but the total data base is inconsistent. The case of caffeine is regulated by food and drug agencies of national governments.

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Date of the literature search (Januar 07, 2000)
Date of last literature search: June 05, 2001

Toxicology

JETOC
RTECS
AGRICOLA
CABA
CANCERLIT
TOXCENTER
TOXLINE
JICST-EPLUS
LIFESCI
TOXLIT
EMBASE
ESBIOBASE
EMBAL
HEALSAFE
CSNB
MEDLINE
IRIS
ATSDR TOX. PROFILES
ATSDR TOX: FAQS
CHEMFINDER
CIVS
GESTIS
GINC
NICNAS
NTP

Oecology

AQUASCI
BIOSIS
EMBASE
ESBIOBASE.
LIFESCI
OCEAN
POLLUAB
SCISEARCH
TOXCENTER
TOXLINE
ULIDAT
DATALOG
CHEMFATE
BIODEG
AQUIRE

HSDB

I U C L I D Data Set

Existing Chemical ID: 58-08-2
CAS No. 58-08-2
EINECS Name caffeine
EC No. 200-362-1
Index number 613-086-00-5
Molecular Formula C8H10N4O2

Producer Related Part
Company: BASF AG
Creation date: 09-DEC-1992

Substance Related Part
Company: BASF AG
Creation date: 09-DEC-1992

Memo: master

Printing date: 04-MAR-2003
Revision date:
Date of last Update: **03-MAR-2003**

Number of Pages: **291**

Chapter (profile): Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile): Reliability: without reliability, 1, 2, 3, 4
Flags (profile): Flags: without flag, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: BASF AG
Contact Person: Product Safety **Date:**
c/o Dr. Hubert Lendle
GUP/Z - Z570
Street: Carl-Bosch-Str
Town: 67056 Ludwigshafen
Country: Germany
Phone: +49 621 60 44712
Telefax: +49 621 60 58043

Flag: Critical study for SIDS endpoint
09-AUG-2001

Type: cooperating company
Name: Bell Flavors & Fragrances, Inc.
Country: United States

Flag: Critical study for SIDS endpoint
06-MAR-2001

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

IUPAC Name: Caffeine
Mol. Formula: C8 H10 N4 O2
Mol. Weight: 194,19 g/mol

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003

1.1.1 General Substance Information

Substance type: natural substance
Physical status: solid
Purity: 98.5 - 100 % w/w

Remark: USP grade with the specification to contain not less than 98.5 and not more than 101% of the ingredient calculated on an anhydrous basis
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (1)

Substance type: natural substance
Physical status: solid

Colour: white
Odour: almost odourless

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

1.1.2 Spectra

1.2 Synonyms and Tradenames

1,3,7-Trimethyl-2,6-dioxopurine

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

1,3,7-trimethyl-2,6-dioxopurine

Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994

1,3,7-Trimethylxanthine

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

1,3,7-trimethylxanthine

Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994

1H-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl- (9CI)

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione

Remark: CAS name
Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994

7-Methyltheophylline

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

Anhydrous caffeine

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-2001

Cafeina

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

Caffein

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

Caffeine (8CI)

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

Coffein, wasserfrei

Flag: non confidential, Critical study for SIDS endpoint
24-MAR-1994

Coffeinum

Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994

Guaranine

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

guaranine

Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994

Koffein

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

Mateina

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

Methyltheobromine

Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994

Methyltheothylline

Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994

Thein

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

Theine

Flag: non confidential, Critical study for SIDS endpoint
09-DEC-1992

1.3 Impurities

Remark: According to USP specification not more than 0.1% residue onignition, 0.5% max. weight loss on drying the anhydrous formand not more than 8.5% of its weight when drying the hydrous form.
Source: Knoll AG Ludwigshafen

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-2001 (1)

1.4 Additives

1.5 Total Quantity

Remark: Consumption World Market (1999): <15.000 t/a
EU-Part: 5.000-10.000 t/a
BRD-Part: 1.000-5.000 t/a
Trend: steady to weakly increasing
Source: Knoll AG Ludwigshafen
Flag: Critical study for SIDS endpoint
26-OCT-2000

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (Xn) harmful
Specific limits: no
R-Phrases: (22) Harmful if swallowed
S-Phrases: (2) Keep out of reach of children

Remark: Index-No.: 613-086-00-5
Flag: non confidential, Critical study for SIDS endpoint
07-MAR-2001 (3)

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: harmful
R-Phrases: (22) Harmful if swallowed

Remark: Index-No.: 613-086-00-5
Flag: non confidential, Critical study for SIDS endpoint
07-MAR-2001 (3)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Wide dispersive use

Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994 (4)

Type: industrial
Category: other

Remark: Beverage industry
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
26-OCT-2000 (4)

Type: use
Category: Cosmetics

Remark: Creams for the treatmant of cellulitis, hair loss, skin aging
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
26-OCT-2000

Type: use
Category: Food/foodstuff additives

Remark: Beverage industry: flavour enhancer, vitalizing drinks
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994 (4)

Type: use
Category: Pharmaceuticals

Remark: Combination with analgesic, stimulant
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
06-MAR-2001 (4)

Remark: Shares on the world market (1999):
Food: 80%
Pharma: 16%
Cosmetics: 3%
Technical application: 1%
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
26-OCT-2000

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

Limit value: other: No components with workplace control parameters.

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

Limit value: other: No MAK- or BAT-value

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (5)

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: other: VwVwS (Germany) of 17.05.1999, Annex 3
Labelled by: other: VwVwS (Germany) of 17.05.1999, Annex 3

Class of danger: 1 (weakly water polluting)

Flag: non confidential, Critical study for SIDS endpoint
04-JUL-2001 (6)

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: EINECS-No. 200-362-1

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (7)

Type: ENCS
Additional Info: ENCS No. 9-419

Remark: ENCS CLASSIFICATION:
Low Molecular Heterocyclic Organic Compounds.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (7)

Type: ECL
Additional Info: ECL Serial No. KE-10766

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (7)

Type: other: SWISS
Additional Info: SWISS No. G-3762

Remark: SWISS CLASSIFICATION:
Giftliste 1 (List of Toxic Substances 1), 31 May 1999.
Toxic Category 3.
Toxicity Category 3 is determined by acute oral lethal doses of 50 - 500 mg/kg in small animals; however, other factors may be taken into consideration regarding data in other types of animals or other affects whether subacute, subchronic or chronic.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (8) (7)

Type: TSCA

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (7)

Type: DSL

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (7)

Type: AICS

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (7)

Type: PICCS

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (7)

1.9.1 Degradation/Transformation Products

EINECS-Name: No hazardous decomposition products known.

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

1.9.2 Components

1.10 Source of Exposure

Remark: Sources of exposure depend on the production procedures and the usage. Caffeine is produced by extraction (direct decaffeination, extraction from tea wastes and dusts and from fractments of tea leaves) and by synthetic processes (methylation of various xanthines). Exposure results from its use as drug or as drug ingredient as well as of caffeine containing food or beverages with a varying content.
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
02-MAR-1994 (4)

1.11 Additional Remarks

1.12 Last Literature Search

Type of Search: Internal and External
Chapters covered: 5.10
Date of Search: 21-OCT-2002

07-FEB-2003

1.13 Reviews

2.1 Melting Point

Value: 235 - 239 degree C

Method: Directive 84/449/EEC, A.1 "Melting point/melting range"

Reliability: (4) not assignable
Manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
28-AUG-2002 (6)

Value: 234 - 239 degree C
Sublimation: yes

Remark: Sublimation at about 180°C
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
07-JUN-2001 (9)

Value: 235 - 237.3 degree C

Method: other

Remark: Method: digital melting point determination method "elektrotermal Series IA 9200"
Reliability: (4) not assignable
secondary quotation
07-JUN-2001 (10)

Value: = 236.8 degree C

Reliability: (4) not assignable
secondary quotation
07-JUN-2001 (11)

Value: = 237 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
04-JUL-2001 (12)

Value: 238 degree C
Decomposition: no at degree C
Sublimation: yes

Remark: Sublimation at 178°C
Reliability: (2) valid with restrictions
Reference Book
07-JUN-2001 (13) (14)

2.2 Boiling Point

Value: = 178 degree C

Decomposition: no

Method: other

Remark: sublimes; pressure cited as 760 mm HG
Reliability: (2) valid with restrictions
Reference Book
Flag: Critical study for SIDS endpoint
07-JUN-2001 (13)

2.3 Density

Type: bulk density
Value: = 600 kg/m3 at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
07-JUN-2001 (12)

Type: density
Value: = 1.23 g/cm³

Remark: Temperature: 19, 18 and 4°C
Reliability: (2) valid with restrictions
Reference Book
Flag: Critical study for SIDS endpoint
28-AUG-2002 (13) (14)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: .000000047 hPa at 25 degree C

Method: other (calculated): MPBPWIN, vers. 1.28

Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
07-JUN-2001 (15)

Value: < .000000013 hPa at 25 degree C

Method: other (calculated)

Remark: Original data: estimated < 1 * 10e-8 mm Hg
Reliability: (2) valid with restrictions
Reference Book
08-JUN-2001 (16) (17)

2.5 Partition Coefficient

log Pow: = -.091 at 23 degree C

Method: other (measured): according to OECD-guidelines of commission

67/548/EWG

GLP: no

Reliability: (1) valid without restriction guideline study
Flag: Critical study for SIDS endpoint
04-JUL-2001 (18)

log Pow: -.07 - .1

Method: other (measured)

Test condition: Shake-flask method and octanol-saturated, kieselguhr-packed column
Reliability: (2) valid with restrictions acceptable publication which meets basic scientific principles
07-JUN-2001 (19)

log Pow: -.05

Method: other (measured)

Test condition: Shake-flask method and HPLC, Temperature 22 to 25°C.
Test substance: analytical grade
Reliability: (2) valid with restrictions acceptable publication which meets basic scientific principles
28-AUG-2002 (20)

log Pow: .61 - .65

Method: other (measured)

Test condition: Automated log P(o/w) measurement (ALPM) utilizing HPLC
Reliability: (2) valid with restrictions acceptable publication which meets basic scientific principles
07-JUN-2001 (21)

Result: The measured octanol/saline partition coefficient is 1.036 (log part. coefficient = 0.0154); the transintegumental tissue uptake index in Schistosoma japonicum ranged between ca. 65 and 75 %; linear regression analysis demonstrated a good correlation between both values.
Reliability: (2) valid with restrictions acceptable publication which meets basic scientific principles
07-JUN-2001 (22)

2.6.1 Solubility in different media

Solubility in: Water
Value: = 1.87 other: %(g/100g) at 16 degree C

GLP: no

Method: visual observation of saturation point
Result:

Temperature °C	caffeine % (g/100g water)	
10.0	1.35	(extrapolated value)
16.0	1.87	
28.0	3.19	
44.1	7.67	
58.7	15.22	
64.9	21.41	
79.0	35.41	
83.9	46.84	
100.3	81.0	(extrapolated value)

Test substance: caffeine (unrefined product)
Reliability: (2) valid with restrictions
comprehensible and scientifically acceptable
Flag: Critical study for SIDS endpoint
12-FEB-2003 (23)

Solubility in: Water
Value: ca. 20 g/l at 20 degree C
pH value: 5.5 - 6.5
Conc.: 10 g/l at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
28-AUG-2002 (6)

Solubility in: Water
Descr.: of low solubility

Result: at 20°C: 22 g/l (1 g/46 ml)
at 80°C: 181 g/l (1 g/5.5 ml)
at 100°C: 666 g/l (1 g/1.5 ml)
Reliability: (2) valid with restrictions
Reference Book
28-AUG-2002 (13)

Solubility in: Water
Value: = 20 g/l at 20 degree C
pH value: = 6.9
Conc.: 10 g/l at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
28-AUG-2002 (12)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

Value:

Result: no self ignition up to the melting point.
Reliability: (2) valid with restrictions
expert judgement
Flag: Critical study for SIDS endpoint
30-SEP-1998 (24)

2.9 Flammability

Result: other

Result: hardly flammable; ignition temperature at or above 540°C (BASF: > 600°C) as measured according to DIN 51 794
Reliability: (4) not assignable
Manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
04-JUL-2001 (6) (12)

Result: not highly flammable
Reliability: (2) valid with restrictions
expert judgement
Flag: Critical study for SIDS endpoint
30-SEP-1998 (24)

2.10 Explosive Properties

Result: not explosive

Remark: not explosive according to the German Blasting Agent Law (Sprengstoffgesetz)
Reliability: (2) valid with restrictions
expert judgement
Flag: Critical study for SIDS endpoint
08-JUN-2001 (24)

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Result: dust explosible
Reliability: (2) valid with restrictions
expert judgement

Flag: Critical study for SIDS endpoint
30-SEP-1998 (24)

Result: Solubility:
freely soluble: pyrrole, tetrahydrofurene containing about 4 % water

	soluble: pyridine, ethyl acetate
	slightly soluble: petroleum ether
	ethanol: ca. 8 g/l at 20 °C; ca. 45 g/l at 60 °C
	acetone: 20 g/l
	chloroform: ca. 180 g/l
	diethyl ether: ca. 1.8 g/l
	benzene: 10 g/l at 20 °C
	ca. 45 g/l in boiling benzene
Reliability:	(2) valid with restrictions
	Reference Book
Flag:	Critical study for SIDS endpoint
07-JUN-2001	(13) (14)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: .0000000000194185 cm³/(molecule * sec)
Degradation: 50 % after 19.8 hour(s)

Method: other (calculated): AOP, vers. 1.87

Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
28-JAN-2003 (15)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: .000000000152 cm³/(molecule * sec)
Degradation: 50 % after 2.5 hour(s)

Method: other (calculated)

Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
07-JUN-2001 (25)

3.1.2 Stability in Water

Type: abiotic
t1/2 pH : > 1 year

Method: other: calculated with HYDROWIN, vers. 1.64

Result: hydrolysis rate is extremely slow
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
28-JAN-2003 (15)

Result: The estimated half-life was 0.8 days in the Rhine river, which was thought to occur as a result of biological removal processes.
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
07-JUN-2001 (26)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: drinking water

Remark: During a two year period caffeine was qualitatively detected in Philadelphia drinking waters
04-JUL-2001 (27)

Type of measurement: background concentration
Medium: other

Result: Caffeine in the order of magnitude of 1 µg/l or > 1 µg/l was detected in sewage effluent or potable water; in the river Lee (UK) 0.29 µg/l was detected.
Test condition: GC analysis
04-JUL-2001 (28)

Type of measurement: background concentration
Medium: other

Remark: Study of organic pollutants in municipal wastewater in Goeteborg, Sweden during 1989 - 1991
Result: The concentration in the influent water ranged between 6 - 30 µg/l and in the effluent water between 0.1 - 0.5 µg/l
Test condition: GC-MS analysis
06-NOV-2000 (29)

Type of measurement: background concentration
Medium: other

Result: Caffeine was detected in the range of 3 - 20 ppb in three POTW facilities
Test condition: Determination by GC-MS in three New Jersey publicly owned treatment works (POTWs)
06-NOV-2000 (30)

Type of measurement: background concentration
Medium: surface water

Result: Caffeine was detected in the Rhine at Lobith at 0.1 µg/l; the estimated half-life was 0.8 days assuming first order reduction process
Test condition: GC-MS analysis
06-NOV-2000 (26)

Type of measurement: concentration at contaminated site
Medium: other

Remark: Concentrations in particulate organic matter in New York city, Jan. - March 1975: 0.7 - 7.0 µg/1000 cu m (equivalent concentration); emissions from coffee-roasting plants are implicated as contributors to ambient air levels
06-NOV-2000 (11)

Type of measurement: other

Medium: other

Remark: Concentrations in primary domestic sewage plant effluent: 0.01 - 0.046 mg/l; concentration in particulate organic matter in New York City, 1-3/1975: 0.7 µg/1000 cu m.
06-NOV-2000 (11)

Type of measurement: other
Medium: other

Remark: Caffeine was detected qualitatively in leachate of a sanitary landfill near Barcelona (Spain)
Test condition: GC-MS analysis
06-NOV-2000 (31)

Type of measurement: other
Medium: other

Remark: Caffeine was identified in base/neutral fractions of Ilona Island wastewater and sludge in the concentration range of 16 - 292 µg/l (19 samples) and the retention time was 16.3 min.
Test condition: GC-MS analysis
06-NOV-2000 (32)

Type of measurement: other
Medium: other

Remark: Concentrations in crude sewage ranged between 10 - 46 ng/l or 10 µg/l and in sewage effluents between 10 - 46 µg/l (USA, sewage and effluents); concentration in sewage effluent at Luton (UK) between 1977 - 1980 was < 1 ng/l; concentration in the Rhine river was 10/1978 0.3 µg/l at Lobith and 2/1978 - 10/1978 between 0.1 - 0.3 µg/l at Maassluis; concentration at percolating filter effluent at Stevenage (UK) between 1977 - 1980 was < 1.0 ng/l; in the Rhine river between 7/21979 - 10/1979 at Lobith 0.1 µg/l, atMaassluis between 7/12979 - 10/1979 between 0.03 - 0.1 µg/l and at Gorinchem in 7/1979 0.03 µg/l.
Source: Knoll AG Ludwigshafen
Test condition: HPLC GC-MS; HPLC-UV; UV-MS; GC-MS
16-MAY-1994 (33)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: adsorption
Media: water - soil
Method: other: calculated with PCKOCWIN, vers. 1.63

Result: estimated log KOC = - 0.0135
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint

28-JAN-2003 (15)

Type: volatility
Media: water - air

Result: Based on the estimated Henry's law constant (H = 1.9*10-19 atm m3/mol) caffeine will not volatize from water to atmosphere.
Reliability: (2) valid with restrictions acceptable calculation method
Flag: Critical study for SIDS endpoint
28-JAN-2003 (34) (35)

Type: adsorption
Media: soil - air

Result: According to the estimated soil adsorption coefficients caffeine will display very high mobility in soil.
Reliability: (2) valid with restrictions acceptable publication which meets basic scientific principles
28-AUG-2002 (35)

Type: adsorption
Media: water - soil

Result: Estimated soil adsorption coefficients ranged from 18 to 22 and indicated that it will not adsorb to sediment and suspended matter (peer reviewed).
Reliability: (2) valid with restrictions acceptable publication which meets basic scientific principles
08-JUN-2001 (21) (16) (17)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level I

Method: Level I - Fugacity-based environmental equilibrium partitioning model, Version 2.11
Result: water: 99.99 %
soil: 0.0064 %
sediment: 0.0065 %

Calculation basis:
water solubility: 20000 g/m3
Vp: 4.70E-6
log Kow -0.09
T: 20 °C
Reliability: (2) valid with restrictions accepted calculation method
Flag: Critical study for SIDS endpoint
28-JAN-2003 (15) (36)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: other: activated sludge from laboratory waste water plants treating municipal sewage
Concentration: 43 mg/l related to Test substance
20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: > 90 - 100 % after 22 day(s)
Result: readily biodegradable

Method: OECD Guide-line 301 A (new version) "Ready Biodegradability: DOC Die Away Test"
Year: 1993
GLP: yes
Test substance: other TS: Theophylline

Result: > 90 % degradation at the end of the 10-days-windowV
Test condition: reference substance: aniline
Test substance: Theophylline shows close structural similarities to caffeine. Thus, this study can be used as analogues for this compound.
Reliability: (1) valid without restriction
Guideline-study
Flag: Critical study for SIDS endpoint
19-FEB-2003 (37)

Type: aerobic
Degradation: 71 % after 28 day(s)
Result: readily biodegradable

Method: OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: As the molecular structure of caffeine and theophylline is very similar and the only difference is an additional methyl group at the nitrogen N7, the classification of caffeine to be readily biodegradable is supported by the degradation result of theophylline which was shown to be readily biodegradable in a DOC Die-away-test (OECD 301A).
Result: Degradation rates in the single assays were 58 % and 84 % BOD/ThOD (NO3) after 28 days after a distinct lag phase, average 71%. The single assays differ by 26%. Nevertheless the criteria for readily biodegradability can be regarded as just reached. This is supported by the result of a study with theophylline (see below).
Reliability: (3) invalid
Guideline study. One of the validity criteria is not fulfilled (the 2 parallels differ by more than 20%).
28-AUG-2002 (38) (39)

Type: aerobic
Result: readily biodegradable

Method: other
Year: 1981

Method: Department of the environment (UK) - Standing Committee of Analysts (1981), Methods for the examination of waters and associated materials: Assessment of biodegradability (1981)
Result: No further information given. The authors discriminate the results of the biodegradation tests as follows: ultimate biodegradation (readily biodegradable, readily biodegradable after acclimatisation, inherently biodegradable), partially biodegradable, persistent (non-biodegradable).
Reliability: (2) valid with restrictions
national standard
Flag: Critical study for SIDS endpoint
28-JAN-2003 (40)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Species: other: fish and aquatic organisms
BCF: .52 - 2.25

Method: other: calculation after Lyman et al. (1990)

Result: estimated
Reliability: (2) valid with restrictions
accepted calculation method
04-JUL-2001 (41) (16) (17)

3.8 Additional Remarks

Remark: Environmental fate/exposure summary:
Caffeine is a naturally occurring and a commercially produced compound; emission into the environment may be as a fugative emission during production or use and in wastewater effluent, landfill leachate or incinerator fly ash; caffeine will display very high mobility if released to soil; volatilization to atmosphere will not occur from either moist or dry soil or water; it has the potential to biodegrade in soil and water; bioaccumulation in fish or adsorption to sediment is not expected; atmospheric caffeine may undergo a gas-phase reaction with photochemically produced hydroxyl radicals at an estimated half-life of 2.5 h; occupational exposure may occur by inhalation of dust or dermal contact during its production, formulation or use; exposure of the general population is by ingestion of foods,medicines or consumer products containing caffeine
Reliability: (4) not assignable
secondary quotation
04-JUL-2001 (42)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 46
LC0: = 46
LC50: ca. 87
LC100: = 215

Method: other: according to DIN 38 412, Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische - Fischtest (L15)
Year: 1982
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Groups of 10 fish were exposed to the test substance at nominal concentrations of 10, 21.5, 46.4, 100, 215, and 464 mg/l. No deaths were observed at 46.4 mg/l and less. Three fish exposed to 100 mg/l died within 24 and another four fish within 48 hours. All fish exposed to 215 mg/l and more died within 1 hour.
Test substance: caffeine (anhydrous); according to the authors, purity was 99.5-100.5%
Reliability: (2) valid with restrictions
test procedure according to national standards (DIN)
Flag: Critical study for SIDS endpoint
28-JAN-2003 (43)

Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 120 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC50: 720

Method: other: according to Birge, W.J. et al.: Environ. Toxicol. Chem. 4, 807-821
Year: 1985
GLP: no data

Result: Teratogenicity screening test (exposure of larvae) using a static renewal procedure, exposure time: 120 hours.
LC50 = 0.72 (0.50-0.94) mg/ml
LC50 = 0.07 (0.04-0.11) mg/ml (malformation)
LOEC = 0.02 mg/ml
TI = 10.29 (teratogenic index = LC50 / EC50)
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
28-AUG-2002 (44)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 3.91
EC50: = 182
EC100: > 500

Method: other: 79/831/EWG, Annexe V, p. C
Year: 1984
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Test condition: Data related to nominal concentrations
Test volume: 10 ml, 4 parallels,
total animals/concentration: 20,
concentration range: 3.95 to 500 mg/l,
check of the study visually after 3, 6, 24 and 48 hours
Reliability: (1) valid without restriction
Guideline-study
Flag: Critical study for SIDS endpoint
28-JAN-2003 (45)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: = 6.25
LOEC: = 12.5
EC10: = 10.2
EC50: > 100
EC90 : > 100

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1984
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: new name of algae: Desmodesmus subspicatus
Test condition: The test substance was tested in the concentration range between 100 and 6,25 mg/l.
The dilution factor was 2.
The analytical verifications of the test substance were investigated at different concentrations in OECD-medium. The analytical results yielded 80% or higher recoveries; they varied between 96,5% and 105,8% of the nominal concentrations at test initiation and between 98,3% and 100,2% at test termination. Therefore, all biological results are related to the nominal concentrations of the

test item.

Reliability: (1) valid without restriction guideline study

28-AUG-2002 (46)

Species: Scenedesmus subspicatus (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: = 6.25
LOEC: = 12.5
EC10: > 100
EC50: > 100
EC90 : > 100

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1984
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: new name of algae: Desmodesmus subspicatus
Test condition: The test substance was tested in the concentration range between 100 and 6,25 mg/l.
The dilution factor was 2.
The analytical verifications of the test substance were investigated at different concentrations in OECD-medium. The analytical results yielded 80% or higher recoveries; they varied between 96,5% and 105,8% of the nominal concentrations at test initiation and between 98,3% and 100,2% at test termination. Therefore, all biological results are related to the nominal concentrations of the test item.
Reliability: (1) valid without restriction
Guideline-study
Flag: Critical study for SIDS endpoint
28-JAN-2003 (47)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 1530
EC50: = 3490
EC90 : = 5240

Method: other: DIN 38412/8 - draft
Year: 1986
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Test condition: Data related to nominal concentrations
test volume: 10 ml, 4 parallels and 1 uninoculated parallel, concentration range: 156 to 10000 ml
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions.
Flag: Critical study for SIDS endpoint

28-JAN-2003 (48)

Type: other
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 5 minute(s)
Unit: mg/l **Analytical monitoring:**
EC50: 603 - 707

Method: other

Test condition: "Microtox" test using an instrument by Beckman company; after reconstitution of the bacteria assay tubes maintained at 15 °C; emission of light was determined by spectrophotometry
Test substance: highest purity available
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
08-JUN-2001 (49)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Species: Oryza sativa (Monocotyledon)
Endpoint: growth

Method: other
Test substance: no data

Result: The effect of caffeine on early development of rice seedlings (growth of roots and shoots) was examined after single or multiple treatment. 0.5 - 10 mM inhibited the growth dose-dependently during the first 5 days. Root growth was more affected than shoot growth. Shoot elongation was inhibited by 50 % at 2.5 mM, whereas root elongation was reduced by about 80 % with one treatment (2.5 mM) or by about 90 % with several treatments. Grain respiration was not affected but the seedlings accumulated caffeine dose-dependently.
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
28-JAN-2003 (50)

Result: Caffeine inhibits growth in seedlings of Coffea arabica.
Reliability: (4) not assignable
secondary quotation
04-JUL-2001 (51)

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

Species: other: beetle
Endpoint: mortality
Expos. period: 20 day(s)
Unit: ppm
LC50: 250.62 - 288

Method: other
Test substance: as prescribed by 1.1 - 1.4

Result: LD50 adults (both sexes): ca. 288 ppm;
LD50 larvae: 250.62 ppm
Test condition: Adults and larvae of the red flour beetle (Tribolium castaneum) were placed in a glass tube containing flour medium treated with caffeine; 30 °C; mortality was assessed after 20 days
Reliability: (2) valid with restrictions

acceptable publication which meets basic scientific principles

Flag: Critical study for SIDS endpoint

28-JAN-2003 (52)

Species: other avian: starling
Endpoint: mortality
Unit: mg/kg bw
LC50: > 500

Method: other: no data

Result: acute oral LD50 >500 mg/kg
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
28-JAN-2003 (53)

Species: other avian: red-winged blackbird
Endpoint: mortality
Unit: mg/kg bw
LC50: = 316

Test substance: other TS

Result: acute oral LD50 = 316 mg/kg
R50 = 13.9 mg/kg (repellency)
hazard factor = R50/LD50 = 0.044
According to the authors, a hazard factor > 1.00 indicates a definite potential for acute oral avian poisoning in the wild; a hazard factor of 0.25 - 1.00 indicates a possible potential; and a hazard factor < 0.25 indicates little or no potential.
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
28-JAN-2003 (53)

Species: other: Xenopus laevis (frog)
Expos. period: 120 hour(s)
Unit: other: mg/l
LC50: = 190

Method: other

Result: Frog Embryo Teratogenesis Assay - Xenopus (FETAX) = teratogenicity screening test (exposure of larvae) using a static renewal procedure
LC50 = 0.19 (0.18-0.21) mg/ml
LC50 = 0.13 (0.12-0.13) mg/ml (malformation)
LOEC = 0.08 mg/ml (MCIG = mean minimum concentration to inhibit growth)
TI = 1.46 (teratogenic index = LC50/EC50)
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
28-AUG-2002 (54) (44)

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

Remark: The highest concentration of the tested 0.04, 0.2 and 1.0 mg/ml of caffeine induced aneuploidy in a short-term hexoploid wheat assay

06-NOV-2000 (55)

Remark: At the tested concentration of 1 mM caffeine was not DNA damaging in an environmental screening assay with the ciliate Tetrahymena pyriformis.

06-NOV-2000 (56)

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex: male/female
Vehicle: water
Value: = 192 mg/kg bw

Method: other
Year: 1959
GLP: no
Test substance: other TS

Remark: Original value: LD50 = 0.192 +/- 0.018 g/kg.
Albino rats were administered the test substance at doses of 0, 160, 180, 200 and 220 mg/kg.
Test substance: caffeine
24-JUL-2002 (57) (58)

Type: LD50
Species: rat
Sex: male
No. of Animals: 5
Vehicle: other: corn oil
Value: = 483 mg/kg bw

Method: other: no data
Year: 1984
GLP: no data
Test substance: other TS

Remark: Groups of 5 male Crl:CD rats (nonfasted) were administered the test substance by gavage at doses of 90, 130, 200, 300, 450, 670, 1000, and 1500 mg/kg and were observed for 14 days. Deaths occurred at doses of 450 mg/kg and more within the days of dosing.
Test substance: caffeine; according to the authors, purity was >99%
06-DEC-2001 (59) (60)

Type: LD50
Species: rat
Sex: male/female
Value: = 233 mg/kg bw

Method: other: no data
Year: 1944
GLP: no
Test substance: other TS

Remark: LD50 = 233 +/- 14 mg/kg.
Test substance: caffeine
06-DEC-2001 (61)

Type: LD50
Species: rat
Sex: male
Value: = 355 mg/kg bw

Method: other: no data
Year: 1978
GLP: no data
Test substance: other TS

Remark: LD50 = 355 (312 - 403) mg/kg.
Test substance: caffeine
06-DEC-2001 (62) (63)

Type: LD50
Species: rat
Sex: female
Value: = 247 mg/kg bw

Method: other: no data
Year: 1978
GLP: no data
Test substance: other TS

Remark: LD50 = 247 (220 - 277) mg/kg.
Test substance: caffeine
06-DEC-2001 (62) (63)

Type: LD50
Species: rat
Value: = 344 mg/kg bw

Method: other: conventional
Year: 1978
GLP: no data
Test substance: other TS

Remark: Original value: LD50 = 0.344 (0.307 - 0.383) g/kg.
LD50 was determined in Sprague-Dawley rats using a conventional method.
Test substance: caffeine
06-DEC-2001 (64)

Type: LD50
Species: rat
Value: = 421 mg/kg bw

Method: other: UP and Down
Year: 1987
GLP: no data
Test substance: other TS

Remark: Original value: LD50 = 0.421 (0.320 - 0.552) g/kg.
LD50 was determined in Sprague-Dawley rats using the Up and

Down method.

Test substance: caffeine

06-DEC-2001 (64)

Type: LD50

Species: rat
Sex: male
Value: = 279 mg/kg bw

Method: other: no data
Year: 1984
GLP: no data
Test substance: other TS

Remark: fasted rats
Test substance: caffeine
06-DEC-2001 (59)

Type: LD50
Species: rat
Sex: male
No. of Animals: 10
Vehicle: other: gum arabic
Value: = 700 mg/kg bw

Method: other: no data
Year: 1989
GLP: no data
Test substance: other TS

Remark: Groups of 10 fasted Sprague-Dawley rats were used. Muscular ridigity and tremor was noted.
Test substance: caffeine
06-DEC-2001 (65)

Type: LD50
Species: rat
Sex: male/female
Value: 50 - 500 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Groups of 3 male and/or female Sprague-Dawley or Wistar rats were used. Daily observations and necropsies were included.
Test substance: caffeine
24-AUG-2000 (66)

Type: LD50
Species: rat
Sex: male/female
No. of Animals: 10
Vehicle: CMC
Value: 261 - 383 mg/kg bw

Method: other: BASF test
Year: 1985
GLP: no

Test substance: as prescribed by 1.1 - 1.4

Remark: Groups of 5 male and 5 female Wistar rats were given a single dose of the test substance at dose levels of 178, 261, and 383 (by gavage; dissolved in 0.5% aqueous carboxymethyl cellulose) and were observed for 14 days. Three males and all females of the high dose group died within the first day after dosing. Pathology revealed general congestive hyperemia in the animals that died; and no abnormalities were found in the survivers.
Reliability: (2) valid with restrictions
comparable to guideline study
Flag: Critical study for SIDS endpoint
06-DEC-2001 (67)

Type: LD50
Species: rat
Sex: male/female
No. of Animals: 12
Vehicle: other: Trioctanoin
Value: 200 - 400 mg/kg bw

Method: other: National Toxicology Program (NTP)
Year: 1982
GLP: yes
Test substance: other TS

Remark: LC50 was between 200 and 400 mg/kg for males and females. Groups of 6 Fischer 344 rats/sex were administered the test substance by gaveage at dose levels of 50, 100, 200, 400, and 800 mg/kg.
The slope of the LC50 curve ws rather steep, especially for males. LD10 was 220 mg/kg for males and 240 mg/kg for females.
Test substance: caffeine; according to the authors, purity was 99.9+% (analyzed)
Reliability: (1) valid without restriction
guideline study (NTP)
Flag: Critical study for SIDS endpoint
06-NOV-2002 (68)

Type: other: ALD
Species: rat
Sex: male
No. of Animals: 1
Vehicle: other: corn oil
Value: = 450 mg/kg bw

Method: other: no data
Year: 1986
GLP: no data
Test substance: other TS

Remark: Determination of the approximate lethal dose (ALD = lowest dose tested which produced death).
One male Crl:CD rat each was were administered the test substance by gavage at doses of 90, 130, 200, 300, 450, 670,

1000, and 1500 mg/kg and was observed for 14 days. Deaths occurred at doses of 450 mg/kg and more within the day of dosing.

Test substance: caffeine; according to the authors, purity was >99%

06-DEC-2001 (60)

Type: LD50
Species: mouse
Value: = 127 mg/kg bw

Method: other: no data
Year: 1978
GLP: no data
Test substance: other TS

Test substance: caffeine
06-DEC-2001 (69)

Type: LD50
Species: mouse
Sex: male/female
No. of Animals: 12
Vehicle: other: sodium benzoate
Value: = 185 mg/kg bw

Method: other: National Toxicology Program (NTP)
Year: 1982
GLP: yes
Test substance: other TS

Remark: LC50 = 185 mg/kg (males and females), 95% confidence limit = 100-240 mg/kg
Groups of 6 B6C3F1 mice/sex were administered the test substance by gavage at dose levels of 125, 250, 500, 750, and 1500 mg/kg.
LD10 was estimated to be 35 mg/kg for males and females.
Test substance: caffeine; according to the authors, purity was 99.9+% (analyzed)
Reliability: (1) valid without restriction
guideline study (NTP)
Flag: Critical study for SIDS endpoint
06-NOV-2002 (70)

Type: other: MTD
Species: mouse
Sex: female
No. of Animals: 10
Vehicle: water
Value: = 200 mg/kg bw

Method: other: no data
Year: 1983
GLP: no data
Test substance: other TS

Remark: The median tolerated dose for a teratogenicity screening test was determined. Groups of 10 nonpregnant CD-1 female mice were administered the test substance for 5 days at one of five dose levels.
Test substance: caffeine

06-DEC-2001 (71)

Type: LD50
Species: rabbit
Value: = 224 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (69)

Species: rabbit
Value: = 246 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (72)

Type: LD50
Species: dog
Value: = 140 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (73)

Type: LD50
Species: guinea pig
Value: = 230 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (74)

Type: LD50
Species: hamster
Value: = 230 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (69)

5.1.2 Acute Inhalation Toxicity

Type:	LC50
Species:	rat
Sex:	male/female
No. of Animals:	10
Vehicle:	other: aerosol
Exposure time:	4 hour(s)
Value:	ca. 4.94 mg/l
Method:	OECD Guide-line 403 "Acute Inhalation Toxicity"
Year:	1988
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4
Remark:	LC 50: ca. 4.94 mg/l (males and females) ca. 4.94 mg/l (males) ca. 4.1 mg/l (females) Groups of 5 Wistar rats/sex were exposed to an aerosol of the test substance (mixed with 2% Aerosil R 972) at nominal concentrations of 2.48 and 4.94 mg/l using a head-nose inhalation system. The rats were exposed for 4 hours and observed for 14 days (day of exposure = day 0). No deaths were observed at the low dose level. In the high dose group, 6/10 animals died. Late deaths were observed; one male each died at day 0 and 7, respectively; 2, 1, and 1 female died at day 0, 1, and 2, respectively. Clinical signs of toxicity included changes in respiration (irregular, accelerated, intermittent, gasping), eyelid closure, salivation, restlessness, attempts to escape, reddish nasal discharge, apathy, and (in the high dose group only) decreased pain reflex and death. Pathology revealed general congestion, bloody ulcers in the glandular stomachs, and/or intensified hyperemia in the animals that died. No pathological changes were observed in the survivers. According to the authors, a third test group (as required by the OECD guideline no. 403) was not included since a third dose level (higher than 4.94 mg/l) was expected to be lethal to all exposed animals.
Test substance:	caffeine (anhydrous powder); according to the authors, purity was 99.5-100.5% referring to dried substance
Reliability:	(2) valid with restrictions OECD guideline study with 2 concentrations only, no GLP,
Flag:	Critical study for SIDS endpoint

06-DEC-2001 (75)

5.1.3 Acute Dermal Toxicity

Type:	LD50
Species:	rat
Sex:	male/female
No. of Animals:	10
Vehicle:	other: olive oil (50% suspension)

Value:	> 2000 mg/kg bw
Method:	other: BASF test
Year:	1988
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4

Remark: Five male and five female Wistar rats were given a 24-h semiocclusive application of a 50% (w/v) aqueous suspension of the test substance (dose level: 2000 mg/kg). After 24 h, the application patches were removed, and the application sites were washed with water. No deaths, signs of toxicity, or local/pathological findings were observed within the 14-day observation period.
Test substance: caffeine (anhydrous powder)
Reliability: (2) valid with restrictions
comparable to guideline study
Flag: Critical study for SIDS endpoint
24-JUL-2002 (76)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Route of admin.: i.p.
Value: = 200 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
29-AUG-2000 (72)

Type: LD50
Species: rat
Route of admin.: i.p.
Value: = 240 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine
18-AUG-2000 (77)

Type: LD50
Species: rat
Route of admin.: i.p.
Value: 200 - 205 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS

Remark: LD50 = 200 mg/kg (1.5-month old rat)
LD50 = 205 mg/kg (2- to 4-month old rat)
Groups of 10-20 rats were administered the test substance at dose levels of 100, 150, 200, 210, 225, 230, and 275 mg/kg. Deaths occurred at doses of 150 mg/kg and more; doses of 230 mg/kg and more were lethal to all animals.
Test substance: caffeine

29-AUG-2000 (78)

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 168 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine

18-AUG-2000 (79)

Type: LD50
Species: guinea pig
Route of admin.: i.p.
Value: = 235 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine

29-AUG-2000 (72)

Type: LD50
Species: rat
Route of admin.: s.c.
Value: = 170 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine

18-AUG-2000 (80)

Type: LD50
Species: mouse
Route of admin.: s.c.
Value: = 242 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine

18-AUG-2000 (81)

Type: LD50
Species: dog
Route of admin.: s.c.
Value: = 100 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
29-AUG-2000 (73)

Type: LD50
Species: rat
Route of admin.: i.v.

Value: = 105 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine
18-AUG-2000 (82)

Type: LD50
Species: mouse
Route of admin.: i.v.
Value: = 100 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
29-AUG-2000 (72)

Type: LD50
Species: mouse
Route of admin.: i.v.
Value: = 62 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
18-AUG-2000 (83)

Type: LD50
Species: rabbit
Route of admin.: i.v.
Value: = 78 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
18-AUG-2000 (84)

Type: LD50
Species: dog
Route of admin.: i.v.
Value: = 175 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
29-AUG-2000 (72)

Type: LD50
Species: guinea pig

Route of admin.: i.v.
Value: = 105 mg/kg bw

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
29-AUG-2000 (72)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: 50 %
Exposure: Semiocclusive
Exposure Time: 4 hour(s)
No. of Animals: 3
PDII: 0
Result: not irritating
EC classificat.: not irritating

Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: 1981
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Two male and one female White Vienna rabbits were applied ca. 500 mg of the test substance (a 50% (w/w) aqueous formulation) for 4 hours under semiocclusive conditions. After 4 hours, the application patches were removed, and the application sites were washed with water and Lutrol/water (1/1). The skin was scored at 30-60 minutes after removal of the patches and at 24, 48, and 72 h. No signs of irritation were observed; irritation indices (erythema and edema) were 0 in each animal at each reading time.
Reliability: (1) valid without restriction
guideline study (OECD)
Flag: Critical study for SIDS endpoint
06-DEC-2001 (85)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Comment: not rinsed
No. of Animals: 3
Result: not irritating
EC classificat.: not irritating

Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"

Year: 1981
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: One tenth millilitre (bulk volume; ca. 56 mg) of the test substance was instilled into the right conjunctival sac of each of 2 male and 1 female White Vienna rabbits. The treated eyes were not washed. The eyes were scored at 1, 24, 48, and 72 h and at 8 days post instillation. Slight corneal opacity was found in asll 3 rabbits at 24h and in 1 rabbit at day 8. Slight to well-defined conjunctival redness was present in all 3 rabbits at 24h (grad 2) and in 1 rabbit at day 8; slight to moderate conjunctival swelling
was found in 1 rabbits at up to 48 hours. No iritis was observed. Mean irritation indices were 0.9 (corneal opacity), 0.0 (iritis), 1.6 (conjunctival erythema), and 0.6 (conjunctival edema).
Reliability: (1) valid without restriction
guideline study (OECD)
Flag: Critical study for SIDS endpoint
08-JUL-2002 (85)

5.3 Sensitization

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: 7 or 8 weeks
Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: ca. 250 mg/kg/d (0.5% in the diet)
Control Group: yes, concurrent no treatment

Method: other: no data
Year: 1984
GLP: no data
Test substance: other TS

Remark: Study of limited value on account of experimental procedure and documentation.
Result: Four groups of rats were fed a diet containing the test substance at concetrations of 0% (control groups) and 0.5% for 7 and 8 weeks. Significant reduction of food consumption and body weight was noted in the two treated groups when compared to their corresponding controls. Absolute weights of testes and thymus were significantly decreased while relative weights were similar to control. Histopathology of the testes revealed scattered areas of vacuolar cell generation in the spermatogenic cells; this degeneration was more pronounced after 8 weeks of feeding.
Test substance: caffeine
Reliability: (3) invalid
only one test concentration
06-DEC-2001 (86)

Species: rat **Sex:** male

Strain: no data
Route of administration: oral feed
Exposure period: 1, 3, 6, 8 months
Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: ca. 70, 140, 280 mg/kg/d(0.125, 0.25, 0.5% in the diet)
Control Group: yes, concurrent no treatment
NOAEL: ca. 70 mg/kg bw

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Result: The testicular effects of the test substance were studied in mature and immature rats. Four-week old rats were fed a diet containing the test substance at concentrations of 0 (control), 0.125, 0.25, and 0.5%. Decreased body weight gain and food consumption was seen at the mid and high dose level. In the high dose group, severely and irreversibly impaired spermatogenesis was observed as early as 1 month; testicular atrophy was observed at 8 months. In the mid dose group, slightly impaired spermatogenesis was seen in ca. 27% of the animals at 6 months. Spermatogonial chromosome damage was not seen. However, there was a trend to decreased mitosis and DNA synthesis in the high dose group at 3 months.
Biochemical parameters were changed at the high dose level. Testicular cAMP was unchanged, dry weight, RNA, DNA and zinc was significantly decreased. Serum cholesterol and testosterone was increased. None of these effects were seen in pair-fed controls. According to the authors, these results indicated that high doses of the test substance produced changes in testicular morphology and composition.
Test substance: caffeine
Reliability: (4) not assignable
abstract only
06-DEC-2001 (87)

Species: rat **Sex:** male
Strain: Sprague-Dawley
Route of administration: drinking water
Exposure period: 6 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 15.4 mg/kg/d (ca. 3.86 mg/rat/d)
Control Group: yes

Method: other: no data
Year: 1989
GLP: no data
Test substance: other TS

Result: The effect of the test substance on the rat pancreas was studied. Male adult rats were given drinking water

containing the test substance for 6 weeks. According to the authors, average daily intake of the test substance was ca. 3.86 mg/rat. Examination of the pancreas revealed no substance-related effect on organ weight or DNA, RNA and protein content while the number of zymogen granules was slightly increased. Amylase, immunoreactive cationic trypsin(ogen), and trypsinogen was elevated in pancreatic homogenate while seerum levels of immunoreactive cationic trypsin(ogen) and amylase were lower than control. The rate of secretion of amylase, trypsin and chymotrypsin was singificantly lower than in controls in response to CCK-8 and nicotine. Leucine incorporation was significantly elevated in acini in the treated rats in the presence of CCK-8, secretin and carbachol.

Test substance: caffeine
Reliability: (4) not assignable
secondary literature

06-DEC-2001 (88)

Species: rat **Sex:** female
Strain: no data
Route of administration: drinking water
Exposure period: before and during pregnancy and during lactation
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 36 mg/kg/d (0.04% in the drinking water)

Method: other: no data
Year: 1990
GLP: no data
Test substance: other TS

Result: The aim of the study was to investigate the effect of maternal caffeine uptake on the tyrosine level in neonatal cerebrum. Dams were administered the test substance at a concentration of 0.04% in the drinking water before and/or during gestation and during lactation. Free amino acids in the cerebrum of the neonates were examined on days 1, 5, and 10 post partum. The tyrosine concentration was increased in the cerebrum (days 1 and 5, with approximate mean caffeine levels of above 1.5-2.0 ug/g wet weight), but not in the liver. The tyrosine level showed a positive correlation with the caffeine level in neonates only on day 1 in the group administered the test substance after pregnancy. There was no significant increase in the fetal cerebral concentration of MOPEG-sulfate. According to the authors, these results suggested that maternal caffeine uptake of the test substance disturbed the neonatal cerebrum through tyrosine and thyrosine hyroxylase and then produced behavioural changes in developing rats.

Test substance: caffeine
Reliability: (4) not assignable
secondary literature

06-DEC-2001 (89)

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: drinking water
Exposure period: 90 days
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: 19.7, 41.8, 85.4, 151.0, 271.9 mg/kg/d (males); 23.1, 51.0, 104.2, 174.2, 287.0 mg/kg/d (females) (188, 375, 750, 1500, 3000 ppm in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL: = 1500 ppm

Method: other: National Toxicology Program (NTP)
Year: 1983
GLP: yes
Test substance: other TS

Result: The aim of this study was to determine the dose levels for a 2-year chronic bioassay. Groups of 12 rats/sex were given the test substance in the drinking water at concentrations of 0 (control), 188, 375, 750, 1500, and 3000 ppm. According to the authors, based on data of body weights and water consumption, the daily doses were calculated to be 0, 19.7, 41.8, 85.4, 151.0, and 271.9 mg/kg for males and 0, 23.1, 51.0, 104.2, 174.2, and 287.0 mg/kg for females. All animals were sacrificed at the end of the treatment period; body and organ weights were recorded. Clinical chemical examinations were performed on animals from the 188, 750, and 3000 ppm and control groups. Microscopic pathology was performed on all lesions appearing grossly and routinely in all major systems in the high dose and control groups.
The body weight gains of all treated groups were decreased. The effect was significant in the highest dose only (reduction of 26%, males, 20%, females). Both food and water consumption was decreased by ca. 10% in this group in both sexes. However, water consumption was increased at 750 ppm (both sexes) and at 375 ppm (females). No significant clinical symptoms were recorded in any group.
Clinical chemistry indicated some significantly increased and/or decreased serum aspartate aminotransferase and alanine aminotransferase values and significantly decreased serum amylase values in treated rats; however, no dose-related patterns were established.
There were no significant treatment-related gross lesions. Microscopic examination revealed alterations (cell enlargement) of the salivary gland which were most marked in the high dose group, diminishing with decreasing dose.
The observed effect in salivary gland was dose dependent in rats and mice in the highest dose group only, the authors gave no description about adverse effect. These is a functional adaptive and reversible effect of salivary glands to well known pharmacological effect of caffeine (sympathicomimetic). The morphological changes correlate to this function are so fare not considered to be an adverse effect of the substance
According to the authors, these results indicated that the maximum tolerated dose to be used for a 2-year chronic

bioassay should be 2000 ppm; doses of 0, 500, 1000, and 2000 ppm were recommended for this study.
Test condition: Groups of 12 animals/sex.
Test substance: caffeine; according to the authors, purity was 99.9% (analyzed)
Reliability: (1) valid without restriction guideline study (NTP)
Flag: Critical study for SIDS endpoint
03-MAR-2003 (90)

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: drinking water
Exposure period: 14 days
Frequency of treatment: continuously in the drinking water
Post exposure period: none

Doses: 15, 31, 62, 123, 245 mg/kg/d (males); 20, 38, 80, 133, 285 mg/kg/d (females) (100, 200, 400, 800, 1600 ppm in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL: > 1500 ppm

Method: other: National Toxicology Program (NTP)
Year: 1983
GLP: yes
Test substance: other TS

Result: The aim of this study was to determine the dose levels for a 90-day study. Groups of 6 rats/sex were given the test substance in the drinking water at concentrations of 0 (control), 100, 200, 400, 800, and 1600 ppm. According to the authors, based on data of body weights and water consumption the daily doses were calculated to be 0, 15, 31, 62, 123, and 245 mg/kg for males and 0, 20, 38 , 80, 122, and 285 mg/kg for females.
No deaths occurred. Rough hair was seen in one male dosed with 200 ppm (day 12); hunched posture was seen in a single 100-ppm female (day 7). No other clinical signs were noted. Body weights and gross pathology revealed no substance-related effect. Microscopic examination of controls and animals treated with 400 ppm and more revealed some changes of the stomach, kidneys, lungs in individual rats administered 800 or 1600 ppm. However, this was not statistically significantly different from control; similar lesions were also found in control rats.
According to the authors, these results suggested that there were no significant dose-related lesions or toxic responses. Based on these results, doses of 0, 188, 375, 750, 1500, and 3000 ppm were selected for the 90-day study.
Test condition: Groups of 6 animals/sex.

Test substance: caffeine; according to the authors, purity was 99.9% (analyzed)
Reliability: (1) valid without restriction
guideline study (NTP)
03-MAR-2003 (91)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: gavage
Exposure period: 100 days
Frequency of treatment: 5 d/w
Post exposure period: none
Doses: 110, 150, 191 mg/kg/d

Method: other: no data
Year: 1967
GLP: no
Test substance: other TS

Remark: Study does not meet current standards; limited value.
Result: CBL Wistar rats were used. The max. LD0 (100 days) or max.

dose that produced no deaths was 110 mg/kg, the LD50 (100 days) was 150 mg/kg and the LD100 (100 days) was 191 mg/kg. Doses in the order of the LD0 (i.e. 110 mg/kg) produced a stressor reaction in the adrenal and thymus glands. Changes in behavior, gastric ulcers, hypertrophic effects in several organs but in general to normal appearance and no changes in growth or eating and drinking habits were noted. Doses in the order of the LD50 (i.e. 150 mg/kg) caused polydypsia and diuresis and some degree of toxic nephritis as well as changes in the liver and other organs.

Test substance: caffeine
Reliability: (3) invalid
06-DEC-2001 (92)

Species: rat **Sex:** no data
Strain: no data
Route of administration: i.p.
Exposure period: 30 days
Frequency of treatment: twice daily
Post exposure period: none
Doses: 10, 25, 50 mg/kg/d
Control Group: yes, concurrent no treatment
NOAEL: = 10 mg/kg bw
LOAEL: = 25 mg/kg bw

Method: other: no data
Year: 1990
GLP: no data
Test substance: other TS

Result: The effect of repeated administration of the test substance on monoamine and monoamine metabolite concentrations in the rat brain was studied. The test substance was administered twice daily for 30 days. Concentrations of brain tissue monoamine, dopamine (DA), norepinephrine (NE), serotonine (5HT), monoamine metabolites, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxy-4-hydroxyphenylglycol (MHPG), and 5-hydroxyindolacetic acid (5HIAA) were determined. No significant changes were found in the low dose group. At the mid dose level, 5HT was significantly increased in striatum while 5HIAA was unchanged. At the high dose level, significant changes were observed with each monoamine system. In striatum, DA and 5HT were increased while DOPAC was decreased. In frontal cortex, NE was increased. In cerebellum, 5HT and MHPG were increased.

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (93)

Species: mouse **Sex:** female
Strain: Balb/c
Route of administration: drinking water
Exposure period: 30 days
Frequency of treatment: continuously in the drinking water

Post exposure period: none
Doses: ca. 100 mg/kg/d (500 mg/l = 500 ppm in the drinking water)
Control Group: yes, concurrent no treatment

Method: other: no data
Year: 1992
GLP: no data
Test substance: other TS

Result: The caffeine-induced enhancement of mammary gland lobulo-alveolar development was studied in ovariectomized, estrogen- and progesterone-treated mice. Thirty mice were administered the test substance at a concentration of 500 mg/l for 30 days (at the days 60 to 90 of age), 31 control mice received tap water. A significant enhancement of lobulo-alveolar development of the mammary gland of the treated mice, compared with controls, was observed. Six blood components, known to enhance normal or neoplastic mammary gland growth processes (total free fatty acids, glucose, IGF-1, insulin, prolactin, and corticosterone) were assesed. Only corticosterone was signifcantly increased in mice treated with the test substance; the other values were similar to control. According to the authors, these results suggested that the enhancement of mammary gland lobulo-alveolar development by chronic consumption of caffeine appeared to be a result of caffeine-enhanced secretion of corticosterone.

While a consistent significant stimulatory effect on mammary lobulo/alveolar differentiation was observed when the test substance was consumed orally, no direct effect on mammary development was seen when the test substance was placed directly into the mammary gland (implantation of a pellet) or in culture media.

Test substance: caffeine
Reliability: (3) invalid
mammary gland examination only
06-DEC-2001 (94) (95)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: drinking water
Exposure period: 90 days
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: 21.4, 43.6, 85.4, 130.5, 167.4 mg/kg/d (males); 24.6, 46.6, 87.9, 134.4, 179.4 mg/kg/d (females) (94, 188, 375, 750, 1500 ppm in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL: 1500 ppm

Method: other: National Toxicology Program (NTP)
Year: 1983
GLP: yes
Test substance: other TS

Result: The aim of this study was to determine the dose levels for a 2-year chronic bioassay. Groups of 12 mice/sex were given the test substance in the drinking water at concentrations of 0 (control), 94, 188, 375, 750, and 1500 ppm. According to the authors, based on data of body weights and water consumption, the daily doses were calculated to be 0, 21.4, 43.6, 85.4, 103.5, and 167.4 mg/kg for males and 0, 24.6, 46.7, 87.9, 134.4, and 179.4 mg/kg for females. All animals were sacrificed at the end of the treatment period; body and organ weights were recorded.

Clinical chemical examinations were performed on animals from the 94, 375, and 1500 ppm and control groups. Microscopic pathology was performed on all lesions appearing grossly and routinely in all major systemsin the high dose and control groups.
Mean body weights were significantly depressed (by >10%) in males treated with 188, 375, and 750 ppm. Final mean body weights were significantly decreased at 94, 188, 375 ppm (both sexes), and at 750 ppm (males only). Food consumption was unaffected. Water consumption was decreased by 10% and more in the groups given 1500 and 750 ppm (both sexes) and increased by 10% and more in all other treated group (both sexes). No significant clinical symptoms were recorded in any group.
Clinical chemistry indicated significant decreases in the levels of serum amylase (1500 ppm, both sexes), serum aspartate aminotransferase (375 ppm, females), and alanine aminotransferase (1500 ppm, females). However, no dose-related trends were indicated.
There were no significant treatment-related gross or microscopic lesions, though microscopic examination revealed some alterations of the salivary gland at the upper limits of normal in the high dose group.
According to the authors, these results indicated that the maximum tolerated dose to be used for a 2-year chronic bioassay should be 1500 ppm; doses of 0, 375, 750, and 1500 ppm were recommended for this study.

Test condition: Groups of 12 animals/sex.
Test substance: caffeine; according to the authors, purity was 99.9% (analyzed)
Reliability: (1) valid without restriction
guideline study (NTP)
Flag: Critical study for SIDS endpoint
03-MAR-2003 (96)

Species: mouse **Sex:** female
Strain: other: TO
Route of administration: dermal
Exposure period: 3 days
Frequency of treatment: twice daily
Post exposure period: none
Doses: 10 and 50 mM solution (ca. 1942, 9710 ug/ml)
Control Group: yes, concurrent vehicle

Method: other: no data
Year: 1984
GLP: no data
Test substance: other TS

Result: The aim of the study was to investigate nuclear enlargement as an early change produced in mouse epidermis by carcinogenic compounds when applied in the presence of a tumor promotor. The test substance was applied to the shaved dorsal skin at concentrations of 10 and 50 mM for 3 days; a

0.1% (v/v) croton oil in methylethylketon was used as solvent. The mice were sacrificed on day 4 of the study. The skin was peeled and examined for enlarged nuclei.

Treatment of the test substance at 10 mM resulted in nuclear enlargement which was just significant at the 5% level. No effect was seen at 50 mM.

Test substance: caffeine
Reliability: (4) not assignable
secondary literature

06-DEC-2001 (97)

Species: hamster **Sex:** male/female
Strain: other: Han:AU
Route of administration: drinking water
Exposure period: 90 days
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 9.0, 24.6, 65.2 mg/kg/d (males); 14.7, 50.8, 104.8 mg/kg/d (females) (91.3, 274, 822 ppm in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL: > 822 ppm

Method: other: no data
Year: 1996
GLP: no data
Test substance: other TS

Result: The aim of the study was to investigate the effect of the test substance on the tyroid. Groups of 20 Syrian golden hamsters/sex were given tap water containing the test substance at concentrations of 0 (control), 91.3, 274, and 822 ppm. Based on data on body weight and water consumption, daily doses were calculated to 0, 9.0, 24.6, and 65.2 mg/kg for males and 0, 14.7, 50.8, and 104.8 mg/kg for females. After 3 months of treatment, groups of 10 animals/sex were sacrificed and autopsied.
Caffeine in plasma (measured at 3 days, 3 weeks and 3 months) was higher in females than in males, due to higher uptake. A transient, non-dose-related increase in mean tri-iodothyronine was seen in mid and high dose males after 3 days of treatment. At later time points, the values were similar in all groups. No treatment-related changes were found in thyroxine (days 3, 24, and 91), and other clinical chemical parameters (day 91), absolute and relative adrenal weight, gross pathology and thyroid histopathology.
According to the authors, in conclusion, no signs of thyroid toxicity of caffeine was seen in Syrian golden hamsters.
Test substance: caffeine, pure, natural (DAB)
06-DEC-2001 (98)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: no data
Metabolic activation: with and without

Result: negative

Method: other: according to Ames, B.N. et al.: Mutat. Res. 347-354
Year: 1984
GLP: no data
Test substance: other TS

Remark: Plate incorporation assay with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor-pretreated Sprague-Dawley rats. Results presented only in tabular form; no further data.
Test substance: caffeine
06-DEC-2001 (99)

Type: DNA damage and repair assay
System of testing: Escherichia coli WP2, WP67, CM871
Concentration: no data
Metabolic activation: with and without
Result: positive

Method: other: no data
Year: 1984
GLP: no data
Test substance: other TS

Remark: DNA repair test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor-pretreated Sprague-Dawley rats; endpoint: bacterial growth; MIC (minimal inhibitory concentration) ranged between 187 and 1125 ug/plate. The test substance induced a nonraparable DNA damage in Escherichia coli.
Results presented only in tabular form; no further data.
Test substance: caffeine
Reliability: (3) invalid
documentation unsufficient
06-DEC-2001 (99)

Type: Ames test
System of testing: Salmonella typhimurium TA97, TA102
Concentration: no data
Metabolic activation: with and without
Result: negative

Method: other: according to Maron, D.M. and Ames, B.N.: Mutat. Res. 113, 173-215
Year: 1984
GLP: no data
Test substance: other TS

Remark: Plate incorporation assay with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor-pretreated Sprague-Dawley rats. Results presented only in tabular form; no further data.
Test substance: caffeine
06-DEC-2001 (100)

Type:	Bacterial forward mutation assay
System of testing:	Salmonella typhimurium BA13
Concentration:	ca. 58, 97, 291, 583, 971, 2524, 2913, 10098, 30100 ug/plate (0.3, 0.5, 1.5, 3, 5, 13, 15, 52, 155 umoles/plate)
Metabolic activation:	without
Result:	negative

Method: other: according to Hera, C. and Pueyo, C.: Mutagenesis 1, 267-273
Year: 1986
GLP: no data
Test substance: other TS

Remark: Salmonella Ara test (preincubation assay) without metabolic activation.
Test substance: caffeine
Reliability: (3) invalid
06-DEC-2001 (101)

Type: other: sporulation test
System of testing: Bacillus subtilis 168DB, BY886
Concentration: 2.5, 5, 7.5, 10 mg/ml
Metabolic activation: without
Result: positive

Method: other: according to Sacks, L.E. and MacGregor, J.T.: Mutat. Res. 95, 191-202
Year: 1982
GLP: no data
Test substance: other TS

Remark: Bacillus subtilis multigene sporulation test. At high concentrations, the test substance was mutagenic.

Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
07-DEC-2001 (102)

Type: other: micronucleus test
System of testing: Rat kidney cell line NRK-49F
Concentration: ca. 971, 1942, 3884 ug/ml (5, 10, 20 mM)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1987
GLP: no data
Test substance: other TS

Remark: The cells were incubated with the test substance for 60 minutes at 37 degree C. At least 4000 interphase cells with visible cytoplasm per treatment were scored. A dose-dependent increase in % cells with micronuclei was seen (ca. 4.5% micronucleated cells at the highest dose level; ca. 0.3% micronucleated cells in controls; result presented graphically).
The test substance was slightly cytotoxic. At a concentration of 10 mM, cell viability was 92.3% and 83.6% of control after 0 and 3 days of incubation, respectively. At a concentration of 20 mM, cell viability was 83.5% and

76.6% of control after 0 and 3 days of incubation, respectively.

Test substance: caffeine

Reliability: (3) invalid
relevant methodical deficiencies, substance was tested in concentration over the level recommended in the OECD/EU guidelines (10mM)
07-DEC-2001 (103)

Type: Cytogenetic assay
System of testing: neural ganglia obtained from Drosophila melanogaster
Concentration: ca. 97, 194, 971, 1942, 3884 ug/ml (0.5, 1, 5, 10, 20 mM)
Metabolic activation: without
Result: ambiguous

Method: other: no data
Year: 1980
GLP: no data
Test substance: other TS

Remark: Third-instar larvae of the wild strain Oregon-R of Drosophila melanogaster were dissected. Neural ganglia were placed in a 0.7% sodium choride solution and treated with the test substance for 2 hours. The ganglia were fixed at set time intervals after treatment for the determination of the effects of the test substance in different stages of the cell cycle. Chromatid aberrations were induced only when the test substance was administered in G2 or approaching mitosis. No aberrations were observed after treatment in S or early G2.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
06-DEC-2001 (104) (105)

Type: Cytogenetic assay
System of testing: Chinese hamster cell line (CHL)
Concentration: 250, 500, 1000 ug/ml
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1977
GLP: no data
Test substance: other TS

Remark: Chromosomal aberration test without metabolic activation, CHL cells were exposed for 24 or 48 h, preparations were made by an air-dry method, 100 metaphases/dose level were evaluated. The test substance produced a dose-related increase in the frequency of chromosomal aberrations at the mid an high dose levels. These concentrations are above the levels recommended in the OECD/EU guidelines (i.e. over the 10 mM level) and could be the reason for the positive results. Negative control and solvent control cultures were included.
Test substance: caffeine
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific

principles. Concentrations are above the levels recommended in the OECD/EU guidelines (i.e. over the 10mM level)
Flag: Critical study for SIDS endpoint
03-MAR-2003 (106) (107)

Type: Ames test
System of testing: Salmonella typhimurium
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1983
GLP: no data
Test substance: other TS

Remark: Preincubation test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats and Syrian hamsters.
Test substance: caffeine

Reliability: (4) not assignable
secondary literature
06-DEC-2001 (108)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: no data
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1977
GLP: no data
Test substance: other TS

Remark: Salmonella typhimurium reverse mutation assay
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (109)

Type: Escherichia coli reverse mutation assay
System of testing: Escherichia coli K12
Concentration: ca. 5000 ug/ml (25.75 mM)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1990
GLP: no data
Test substance: other TS

Remark: Inductions of frameshift mutation was observed in strains of Escherichia coli K12.

Test substance: caffeine
Reliability: (3) invalid
only one concentration tested
06-DEC-2001 (110)

Type: Bacillus subtilis recombination assay
System of testing: Bacillus subtilis 17A (Rec+), 45T (Rec-)
Concentration: ca. 1000 ug/ml
Metabolic activation: without
Result: ambiguous

Method: other: no data
Year: 1972
GLP: no
Test substance: other TS

Remark: Recombination test without metabolic activation; mutagenicity was indicated by growth inhibition. No growth inhibition was seen in tester strain 17A; borderline activity was seen in tester strain 45T.
Test substance: caffeine
Reliability: (3) invalid
06-DEC-2001 (111)

Type: Bacterial forward mutation assay
System of testing: Salmonella typhimurium
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1978
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (112)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, 1530, hisG46
Concentration: 6000 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1975
GLP: no
Test substance: other TS

Remark: Salmonella typhimurium reverse mutation assay; <70 revertants/plate were noted
Test substance: caffeine
Reliability: (3) invalid

06-DEC-2001 (113)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA 535, TA1537, TA1538
Concentration: up to 1940 ug/plate (up to 10 umoles/plate)
Metabolic activation: with and without
Result: negative

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1979
GLP: no data
Test substance: other TS

Remark: Ames test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats.

Test substance: caffeine; according to the authors, purity was of the finest pure grade

06-DEC-2001 (114)

Type: Salmonella typhimurium reverse mutation assay
System of testing: Salmonella typhimurium TA92
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Salmonella typhimurium reverse mutation assay
Test substance: caffeine
Reliability: (4) not assignable

06-DEC-2001 (115)

Type: Escherichia coli reverse mutation assay
System of testing: Escherichia coli K12 ND 160
Concentration: 1000 ug/ml
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine
Reliability: (3) invalid
no further data

06-DEC-2001 (116) (117)

Type: Bacterial forward mutation assay
System of testing: Escherichia coli K12 (343/113)
Concentration: up to 1940 ug/plate (up to 10 umoles/plate)
Metabolic activation: with and without

Result: negative

Method: other: according to Mohn and Ellenberger in: Kilbey, B.J. et al. (eds.): Handbook of mutagenicity test procedures, Elsevier, Amsterdam; pp. 95-118
Year: 1977
GLP: no data
Test substance: other TS

Remark: Test on mutations to 5-methyltryptophan resistance, arginine galactose utilization and arginine independence with and without metabolic activation with S-9 mix prepared from liver homogenate of male NMRI mice.
Test substance: caffeine; according to the authors, purity was of the finest pure grade
Reliability: (2) valid with restrictions

06-DEC-2001 (114)

Type: Bacterial gene mutation assay
System of testing: Escherichia coli
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: Endpoints:
- Phage T5 resistance (Novick and Szilard, 1951; Kubitschek and Bendigkeit, 1958)
- Phage resistance (Gezelius and Fries, 1952; Glass and Novick, 1959)
- Methionine and tryptophan independence (Greer, 1958)

Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (118) (119) (120) (121) (122)

Type: Bacterial gene mutation assay
System of testing: Escherichia coli
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1958
GLP: no
Test substance: other TS

Remark: Endpoint: Streptomycin dependence
Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (123)

Type: Bacterial gene mutation assay
System of testing: Klebsiella pneumoniae
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1969
GLP: no
Test substance: other TS

Test substance: caffeine
06-DEC-2001 (124)

Type: other
System of testing: miscellaneous test systems

Test substance: other TS

Remark: A summary on mutagenicity data was given.
Caffeine

- was generally mutagenic in algae;
- negative and positive in fungi;
- negative in Schizosaccharomyces pombe (however, meiotic recombination was decreased mitotic gene conversion was increased in this yeast);
- induced aneuploidy in Saccharomyces cerevisiae;
- increased the rate of point mutations in plants (Glycine max.);
- induced chromosomal aberrations in plants (Allium, Hordeum and Vicia species) with few exceptions;
- induced sister chromatid exchange in Vicia faba;
- induced recombination in some plant studies (Glycine max. and Nicotiana tabacum).

Test substance: caffeine

30-AUG-2000 (72)

Type: DNA damage and repair assay
System of testing: Chinese hamster ovary (CHO) cells
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature

06-DEC-2001 (125)

Type: DNA damage and repair assay
System of testing: Chinese hamster V79 cells
Concentration: ca. 583, 1942, 5826 ug/ml (3, 10, 30 mM)
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1976
GLP: no
Test substance: other TS

Remark: Alkaline Elution Test, 2-hour incubation.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature

06-DEC-2001 (126) (127)

Type: DNA damage and repair assay
System of testing: Syrian hamster embryo (SHE) cells
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1976
GLP: no data

Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (128)

Type: Unscheduled DNA synthesis
System of testing: Syrian hamster embryo (SHE) cells
Metabolic activation: without

Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (128)

Type: Mammalian cell gene mutation assay
System of testing: Chinese hamster cells (CHO, V79)
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Gene mutation assays in CHO cells and V79 cells
Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (129) (130) (131) (132) (133)

Type: Sister chromatid exchange assay
System of testing: various Chinese hamster cells
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Don and Cl-1 cells were used.
Test substance: caffeine
06-DEC-2001 (134) (135)

Type: Sister chromatid exchange assay
System of testing: Mouse blastocysts
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (136)

Type: Cytogenetic assay
System of testing: various Chinese hamster cells

Metabolic activation: without
Result: positive

Method: other: no data
GLP: no

Test substance: other TS

Remark: CHO, CHL, Cl-1 and endoreduplicated cells were used.
Test substance: caffeine
Reliability: (4) not assignable
secondary test system
06-DEC-2001 (132) (137) (138) (139) (140)

Type: Cytogenetic assay
System of testing: human HeLa cells, rat MCTI cells
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
unsuitable test system
06-DEC-2001 (141)

Type: Cytogenetic assay
System of testing: various Human cells
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Human lymphocytes, HeLa cells, Fanconi's anemia lymphocytes, and leukocytes were used.
Test substance: caffeine
Reliability: (4) not assignable
unsuitable test system
06-DEC-2001 (142) (143) (144) (145) (146)

Type: other: cell transformation test
System of testing: various cells
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: Syrian hamster embryo cells, hamster embryo cells and mouse C3H2K cells were used.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (128) (147) (148)

Type: Unscheduled DNA synthesis
System of testing: human lymphocytes
Concentration: ca. 97, 146, 194, 388, 583 ug/ml (0.5, 0.75, 1.0, 2.0, 3.0 mM)
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Remark: DNA repair test using lymphocytes obtained from healthy donors and from patients with systemic lupus erythematosus (SLE; reduced levels of excision repair). The test substance did not inhibit DNA repair in normal lymphcytes and did not further reduce DNA repair in SLE cells).
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
07-DEC-2001 (149)

Type: Mammalian cell gene mutation assay
System of testing: various Human cells
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Remark: Human lymphoblast MIT 2 and HH-4 cells
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
06-DEC-2001 (112)

Type: Sister chromatid exchange assay
System of testing: various Human cells
Metabolic activation: without
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Human lymphocytes, fibroblasts and XP lymphoblastoid cells were used. Most of the results were positive.
Test substance: caffeine
31-AUG-2000 (150) (151) (152) (153) (154) (155) (156)

Type: other
System of testing: Photobacterium leiognathi
Metabolic activation: without

Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Bioluminescence assay; 2 mg/ml induced a rapid luminescence within 30 min; the minimal concentration that reacted positive in this assay was 20 µg/ml.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
07-DEC-2001 (157)

Type: Mammalian cell gene mutation assay
System of testing: Chinese hamster V79 cells
Concentration: ca. 194 ug/ml (1.0 mM)
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: No induction of ouobain-resistant mutants was induced by the test substance.
Test substance: caffeine, reagent grade
22-AUG-2000 (158)

Type: Sister chromatid exchange assay
System of testing: Chinese hamster V79 cells
Concentration: ca. 194 ug/ml (1.0 mM)
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Test substance: caffeine, reagent grade
Reliability: (3) invalid
only one concentration tested
07-DEC-2001 (158)

Type: Cytogenetic assay
System of testing: Allium proliferum
Concentration: ca. 1940, 3880 ug/ml (10, 20 mM)
Metabolic activation: no data
Result: positive

Method: other: no data
Year: 1971
GLP: no
Test substance: other TS

Remark: Chromosomal aberration test. Positive results were observed at concentrations of 10 and 20 mM. The results were dependent on temperature and ATP content.
Test substance: caffeine
06-DEC-2001 (159) (160)

Type: Cytogenetic assay
System of testing: human peripheral blood leukocytes
Concentration: 0.05, 0.1, 0.25, 0.5, 1.0 ug/ml (0.005, 0.01, 0.025, 0.05, 0.1%)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1971
GLP: no
Test substance: other TS

Remark: Chromosomal aberration test, incubation during the last 24 h of a 72-hour culture. Chromosomal damage was confined to DNA-synthesis phase, S-phase was most sensitive, G1 and G2 phase were not affected.
Test substance: caffeine
Reliability: (3) invalid
no detailed data are given
06-DEC-2001 (161)

Type: Cytogenetic assay
System of testing: human embryonic fibroblasts
Concentration: 0.05, 0.1, 0.25, 0.5, 1.0 ug/ml (0.005, 0.01, 0.025, 0.05, 0.1%)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1971
GLP: no
Test substance: other TS

Remark: Chromosomal aberration test, incubation during the last 24 h of a 72-hour culture. Chromosomal damage was confined to DNA-synthesis phase, S-phase was most sensitive, G1 and G2 phase were not affected. Chromatid aberrations were predominandly gaps and breaks, no exchanges were observed.
Test substance: caffeine
Reliability: (3) invalid
without metabolic activation only
06-DEC-2001 (161)

Type: Cytogenetic assay
System of testing: human colon carcinoma LIM cells (1215/neo, 1215/wt, 1215/248, 1215/273, SW480)
Concentration: ca. 390 ug/ml (2 mM)
Metabolic activation: without

Result: ambiguous

Method: other: no data
Year: 1996
GLP: no data
Test substance: other TS

Remark: Chromosomal aberration test without metabolic activation using human hereditary non-polyposis colon carcinoma cell lines with various p53 (tumor-suppressor gene) status. Expression of p53 was measured by Western-blot analysis. Treatment with the test substance for 2 h enhanced the frequency of chromosomal breaks in all cell lines. No increase in the number of cells with numerical chromosome changes was seen in cell lines 1215/neo, 1215/273, and SW480. In SW480 cells, the incidence of polyploid cells was 2-fold of control. An increase in the number of hyperdiploid cells was only seen in LIM1215/248 cells.
Test substance: caffeine

Reliability: (3) invalid
tumor cell line, unsuitable test system
06-DEC-2001 (162)

Type: Cytogenetic assay
System of testing: human lymphocytes
Concentration: 5, 10, 25, 50, 75, 100 ug/ml
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1985
GLP: no data
Test substance: other TS

Remark: Chromosomal aberration test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated animals. The test substance did not statistically significantly increase any type of aberrations when compared with negative control (water); positive control: 40 ug/culture endoxan.
Test substance: caffeine

Reliability: (2) valid with restrictions
acceptable, well documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
06-DEC-2001 (163)

Type: Yeast gene mutation assay
System of testing: Saccharomyces cerevisiae D6
Concentration: no data
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Remark: Aneuploidy test in growing cells without metabolic activation.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (164)

Type: other: reverse mutation test
System of testing: Neurospora crassa
Metabolic activation: no data
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: The test substance induced meiotic nondisjunction producing n+1 acespores in growing cultures.
Test substance: caffeine

Reliability: (3) invalid
unsuitable test system
07-DEC-2001 (165) (166)

Type: Cytogenetic assay
System of testing: Chinese hamster cells
Concentration: ca. 4850 ug/ml (25 mM)
Metabolic activation: no data
Result: positive

Method: other: no data
Year: 1971
GLP: no
Test substance: other TS

Remark: Chromosomal aberration test. A positive result was observed at a concentration of 25 mM. The result depended on temperature but not on ATP content.
Test substance: caffeine
Reliability: (3) invalid
one concentration only, the concentration was over the level recommended in OECD guideline (10 mM)
06-DEC-2001 (160)

Type: Cytogenetic assay
System of testing: Vicia faba
Metabolic activation: no data
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: Summary of four different studies. The test substance was mutagenic in three studies (Kaul and Zutshi, 1973; Oseicka, 1976; Somborska-Ciania et al., 1974) and not mutagenic in one study (Swietlinska et al., 1973).
Test substance: caffeine
30-AUG-2000 (167) (168) (169) (170)

Type: other: somatic mutation in plant
System of testing: Tradescantia clone 4430
Concentration: ca. 194 ug/ml (1 mM)
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: The liquid test substance was negative after chronic exposure at 1 mM in the Tradescantia assay (hybrid clone 4430) for testing mutagens
Test substance: caffeine
Reliability: (3) invalid

unsuitable test system
07-DEC-2001 (171)

Type: other: somatic mutation in plant
System of testing: Glycine max (L.) merill
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: The test substance was positive in the soybean (Glycine max merrill) spot test as a short-term assay for environmental mutagens.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
07-DEC-2001 (172)

Type: Yeast Cytogenetic assay
System of testing: Schizosaccharomyce pombe
Concentration: ca. 1 ug/ml (0.1%)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1974
GLP: no
Test substance: other TS

Remark: The tested substance reduced the number of single and double crossing-over recombinants in in chromosome II and affected the gene conversion frequency at the ade7 locus.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
07-DEC-2001 (173)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1538
Concentration: 4, 20, 100, 500, 2500 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no data
Test substance: other TS

Remark: Ames test (pour-plate method) with and without metabolic activation with X-9 mix prepared from liver homogenate of Aroclor-pretreated rats.
Test substance: caffeine
23-AUG-2000 (174)

Type: Cytogenetic assay

System of testing:	human HeLa cells
Concentration:	40, 60, 80, 120, 140, 160 ug/ml
Metabolic activation:	without
Result:	positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: After 1-4 weeks of treatment, a significant and concentration-related increase in the frequency of terminal breaks was seen in HeLa cells at concentrations of 40 ug/ml and above.
Test substance: caffeine
Reliability: (3) invalid
tumor cell line, unsuitable test system
06-DEC-2001 (175)

Type: Cytogenetic assay
System of testing: rat MCTI cells
Concentration: 40, 60, 80, 120, 140, 160 ug/ml
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Remark: After 1-4 weeks of treatment, MCTI cells only showed minimal effects at all concentrations tested.
Test substance: caffeine
Reliability: (3) invalid
tumor cell line, unsuitable test system
06-DEC-2001 (175)

Type: Sister chromatid exchange assay
System of testing: skin fibroblasts of the Indian muntjac
Concentration: 100 ug/ml
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Remark: The frequency of SCE was almost doubled in the presence of the test substance.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (176)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1536, TA1537, TA1538
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1977
GLP: no
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (177)

Type: Yeast gene mutation assay
System of testing: Saccaromyces cerevisiae D3
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (177)

Type: Bacterial gene mutation assay
System of testing: Escherichia coli B/Sd-4/1,3,4,5 and B/Sd-4/3,4
Result: positive

Method: other: no data
Year: 1951
GLP: no
Test substance: other TS

Test substance: caffeine
06-DEC-2001 (178)

Type: Cytogenetic assay
System of testing: rat liver epithelial cells
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
unsuitable test system
06-DEC-2001 (179)

Type: Sister chromatid exchange assay
System of testing: rat liver epithelial cells
Metabolic activation: without
Result: negative

Method: other: no data

Year: 1980
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (179)

Type: Bacterial gene mutation assay
System of testing: Escherichia coli PolA+, PolA-
Concentration: 6000 ug/well
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: Inhibition zone was 5 and 11 mm for tester strain PolA+ and PolA-, respectively.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (180)

Type: DNA damage and repair assay
System of testing: Escherichia coli WP2, WP-B
Concentration: ca. 1550 ug/ml (8 mM)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1972
GLP: no
Test substance: other TS

Remark: Excision repair and recombination repair test in the presence and absence of UV irradiation.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (181)

Type: other: DNA binding
System of testing: Escherichia coli
Concentration: ca. 3884, 9710 ug/ml (20, 50 mM)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1971
GLP: no
Test substance: other TS

Remark: Binding to single strand DNA, but not to double strand DNA was seen.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (182)

Type: Unscheduled DNA synthesis
System of testing: rat tracheal epithelium (cultured)

Concentration: ca. 19 - 1942 ug/ml (0.1 - 10 mM)
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1981
GLP: no data
Test substance: other TS

Remark: Rings of trachea from 8-week old male F344 rats were incubated for 2 hours at 37 degree Centigrade containing 10uCi/ml (methyl-3H)dTd and the test substance. No induction of UDS was observed.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (183)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1537
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1980
GLP: no data
Test substance: other TS

Remark: Preincubation test with and without metabolic activation with rats liver S-9.
Test substance: caffeine
Reliability: (3) invalid
06-DEC-2001 (184) (185)

Type: Cytogenetic assay
System of testing: Chinese hamster lung fibroblasts
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Chromosomal aberration test with and without metabolic activation with rat liver S-9.
Test substance: caffeine
Reliability: (4) not assignable
unsuitable test system
06-DEC-2001 (184) (186) (185)

Type: Cytogenetic assay
System of testing: Chinese hamster cells
Concentration: ca. 194 - 777 ug/ml (1 - 4 mM)
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: The frequency of chromosomal aberrations increased in a dose-related manner.
Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (187)

Type: Sister chromatid exchange assay
System of testing: Chinese hamster cells
Concentration: ca. 194 - 777 ug/ml (1 - 4 mM)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1974
GLP: no
Test substance: other TS

Remark: The frequency of SCEs increased gradually with the dose.
Test substance: caffeine
07-DEC-2001 (188)

Type: other: Rec-assay
System of testing: funghi
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (189)

Type: other: micronucleus test
System of testing: preimplantation mouse embryo (two-cell stage)
Concentration: ca. 24, 49, 97, 194, 388, 777, 971, 1359 ug/ml (0.125, 0.25, 0.5, 1, 2, 4, 5, 7 mM)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1985
GLP: no data
Test substance: other TS

Remark: A linear increase in the number of microneuclei was seen at concentrations of 1 mM (ca. 194 ug/ml) and more. Caffeine did not induce micronuclei if the concentration was 1 mM or less.
Test substance: caffeine
Reliability: (3) invalid
inconsistent results
07-DEC-2001 (190)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538; Escherichia coli WP2 uvrA
Metabolic activation: with and without

Result: negative

Method: other: no data
Year: 1981
GLP: no data

Test substance: other TS

Remark: Ames test with and without metabolic activation with S-9 mix prepared from rats, hamsters, and mice.
Test substance: caffeine
Reliability: (4) not assignable
06-DEC-2001 (191)

Type: other: umu test
System of testing: Salmonella typhimurium TA1535/psk 1002
Concentration: 1670 ug/ml
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
24-AUG-2000 (192)

Type: other: SOS test
System of testing: Escherichia coli PQ37 (sulA::lacZ, Pho(c))
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1985
GLP: no data
Test substance: other TS

Remark: No inhibiton of SOS induction or protein synthesis was observed.
Test substance: caffeine
Reliability: (4) not assignable
abstract, documentation insufficient for assessment
07-DEC-2001 (193)

Type: other: spindel disturbance
System of testing: Chinese hamster (V79) cells
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Effects on survival, aneuploidy, sulfhydryl and ATP measurements and on C-mitotic activity were studied. Subtle disturbance (partial C-mitosis) was seen.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
07-DEC-2001 (194)

Type: other: cell transformation
System of testing: Syrian hamster embryo (SHE) cells
Concentration: 1 - 250 ug/ml
Metabolic activation: without

Result: negative

Method: other: no data
Year: 1983
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (3) invalid
documentation insufficient for assessment
07-DEC-2001 (195) (196)

Type: Cytogenetic assay
System of testing: human lymphocytes
Concentration: ca. 485, 971 ug/ml
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: The test substance increased the frequency of chromatid breakage and decreased G2 duration in X-ray irradiated and nonirradiated cells.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
06-DEC-2001 (197)

Type: other: SOS Chromotest
System of testing: Escherichia coli PQ37
Result: negative

Method: other: no data
Year: 1985
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (198)

Type: other: micronucleus test
System of testing: human hepatoma (Hep-G2) cells
Concentration: 5, 50, 500 ug/ml
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1981
GLP: no data
Test substance: other TS

Remark: Dose-related increase in the number of micronuclei was seen in all treated cells (incubation for 24 hours; scoring of 1000 cells/dose level).
Test substance: caffeine
Reliability: (4) not assignable
abstract
07-DEC-2001 (199)

Type: other
System of testing: Simian Virus (SV) 40
Concentration: ca. 0.2 - 29 mg/ml (10 - 150 mM)
Metabolic activation: without
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: The inibitory effect of the test substance on type I and type II topoisomerases was evaluated as judged by its effect on replicating SV40 chromosmes.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
07-DEC-2001 (200)

Type: Escherichia coli reverse mutation assay
System of testing: Escherichia coli Ds-4-73
Metabolic activation: without
Result: negative

Method: other: no data
Year: 1958
GLP: no
Test substance: other TS

Remark: Test on reversion from streptomycin dependence to independence, paper disc method.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
06-DEC-2001 (201)

Type: other: test on mitotic activity
System of testing: human peripheral blood lymphocytes
Concentration: ca. 19, 194, 1942 ug/ml (0.1, 1, 10 mM)
Metabolic activation: without

Method: other: no data
GLP: no
Test substance: other TS

Remark: The effect of the test subtance on mitosis was studied. At 0.1 mM, mitotic rate averaged 111% of control rate. The rate

was 192% in blood samples from females and 68% in blood samples from males; this differenc was statistically significant. At 1 mM, mitotic rate was 41% of control (antimitotic activity). At 10 mM, mitotic rate was 0 (cytostatic activity). No chromosome damage was observed.

Test substance: caffeine

Reliability: (3) invalid
unsuitable test system

07-DEC-2001 (202)

Type: Sister chromatid exchange assay
System of testing: human xeroderma pigmentosum cell lines (XP19, XP20)
Concentration: ca. 19, 97, 194 ug/ml (0.1, 0.5, 1.0 mM)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1988
GLP: no data
Test substance: other TS

Remark: A marked increase in the frequency of SCE was observed at concentrations of 0.1 to 1 mM in both cell lines.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system, tumor cell line
07-DEC-2001 (203)

Type: Cytogenetic assay
System of testing: human diploid fibroblasts (WI-38)
Concentration: ca. 252, 505, 757 ug/ml (1.3, 2.6, 3.9 mM)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1977
GLP: no
Test substance: other TS

Remark: Mitotic index was reduced to 58.8% at 1.3 mM with significant clastogencity (breaks and gaps); no exchange figures were seen (incubation with the test substance for 24 h, colcemid added 24 h later, scoring of 200 metaphases per concentration).
Test substance: caffeine
Reliability: (3) invalid
documentation unsufficient
06-DEC-2001 (204)

Type: Cytogenetic assay
System of testing: human diploid fibroblasts (WI-38)
Concentration: ca. 1.0, 1.5, 2.0 mg/ml (5.1, 7.7, 10.3 mM)
Metabolic activation: with and without
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: Cytogenetic assay with and without metabolic activation with S-9 mix prepared from livers of Aroclor-pretreated rats (incubation for 24 h, then incubation with the test substance in the presence and absence of S-9 for 1 h, colcemid added 24 h later, scoring of 100 metaphases per

concentration). A significant increase in chromsome breaks was observed only at the high concentration in the presence of S-9. No exchange figures were seen with and without S-9.

Test substance: caffeine

Reliability: (3) invalid
documentation unsufficient
06-DEC-2001 (205)

Type: Cytogenetic assay
System of testing: human lymphocytes
Concentration: 250, 500, 750 ug/ml
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1975
GLP: no
Test substance: other TS

Remark: A significant increase in chromosome abnormalites (breaks) was noted at 500 ug/ml and above. Mitotic indices were reduced at 500 ug/ml and above. Results are available in a graphical manner only.
Test substance: caffeine
Reliability: (2) valid with restrictions
06-DEC-2001 (206)

Type: other: cell transformation
System of testing: Syrian hamster cells, BHK 21cl13
Metabolic activation: with and without
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Soft agar assay.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
07-DEC-2001 (117)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: 100, 333.3, 1000, 3333.3, 10000 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: National Toxicology Program (NTP)
Year: 1986
GLP: no data
Test substance: other TS

Remark: Preincubation test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats and male Syrian hamsters. Solvent (DMSO) controls and positive controls were included. For positive control, 2-aminoanthracene (all tester strains with metabolic activation), sodium azide

(TA1535 and TA100 -S-9), 9-aminoacridine (TA1537 -S-9), and 4-nitro-o-phenylenediamine (TA98 -S-9) was used.

Test substance: caffeine; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
comparable to guideline study
Flag: Critical study for SIDS endpoint
06-DEC-2001 (207)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538; Escherichia coli WP2 uvrA (trp-)
Concentration: 3.3, 10, 33.3, 100, 333.3, 1000, 3333.3 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: National Toxicology Program (NTP)
Year: 1985
GLP: no data
Test substance: other TS

Remark: Bacterial reverse mutation test with and without metabolic activation with S-9 mix prepared from liver homogenate of both untreated and Aroclor 1254-pretreated male Fischer 344 rats, male BbC3F1 mice, and male Syrian hamsters. Solvent (distilled water, DMSO) controls and positive controls were included. For positive control, 2-nitro-fluorene (TA98 and TAS1538 -S-9), sodium azide (TA100 and TA153 -S-9), 9-aminoacridine (TA1537 -S-9), 2-aminoanthracene (all Salmonella strains with metabolic activation), N-methyl-N'-nitro-N-nitrosoguanidine (E. coli -S-9), and (2-2(furyl)-3-(5-nitro-2-furyl)acrylamide = Aflatoxine 2 (E. coli +S-9) was used.
Test substance: caffeine; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
comparable to guideline study
Flag: Critical study for SIDS endpoint
06-DEC-2001 (208)

Type: Mouse lymphoma assay
System of testing: L5178Y cells
Concentration: ca. 2950, 3555, 4270, 5125, 6155, 7380, 8855, 10620 ug/ml (15.2, 18.3, 22.0, 26.4, 31.7, 38.0, 45.6, 54.7 mM)
Metabolic activation: without
Result: negative

Method: other: according to Clive, D. and Spector, J.F.S.: Mutat. Res. 31, 17-29
Year: 1975
GLP: no data
Test substance: other TS

Remark: Point mutation test without metabolic activation, incubation time: 2 hours; cell viability declined in a dose-dependent manner with the highest concentration being lethal to all exposed cells.
Test substance: caffeine

Reliability: (2) valid with restrictions
acceptable, well documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
30-AUG-2000 (209)

Type: Sister chromatid exchange assay
System of testing: V79 cells
Concentration: up to 1.6x10e2 M (3.1 mg/ml)
Metabolic activation: without
Result: ambiguous

Method: other
Year: 1986
GLP: no data
Test substance: other TS

Remark: Different study protocol were used, A: exposure to caffeine for 3h before addition of BrdU, B: exposure for 24h before addition of BrdU, C: chronic exposure for 24h in presence of BrdU, D: exposure to caffeine during the first cell cycle (10h) in the presence of BrdU, followed by cultivation in BrdU-free medium for 13h. E: exposure during the second cell cycle. BrdU for 10h and then to caffein for 13h in BrdU-free medium.
Result: The chronic treatment and the treatment during the second cell cycle in the presence produce SCE only.No SCE induction was found, when cells with normal DNA were treated for 3 and 24h.
06-DEC-2001 (210)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: mouse **Sex:** female
Strain: ICR
Route of admin.: i.p.
Exposure period: single dose
Doses: 150 mg/kg
Result: negative

Method: other: according to Mailhes, J. and Yuan, Z.P.: Gamete Res. 17, 77-83
Year: 1987
GLP: no data
Test substance: other TS

Result: The aim of the study was to investigate the ability of the test substance to induce aneuploidy in mammalian oocytes. Following superovulation, groups of 10 or 20 females mice were given an i.p. injection of the test substance at various times prior to metaphase I (MI). Ovulated oocytes were collected from the oviducts and processed for cytogenetic analysis. Statistical analysis of the frequencies of hyperploid, MI, diploid, premature centromere

separation and single chromatids revealed non-significant differences between control and treated groups. Structural chromosomal aberrations were not seen. According to the authors, these results indicated that the test substance neither retarded the rate of oocyte meiotic maturation nor increased the incidence of aneuploidy in mouse oocytes.

Test condition: Groups of 10 or 20 female mice.

Test substance: caffeine

Reliability: (2) valid with restrictions
acceptable, well documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
11-SEP-2000 (211)

Type: Cytogenetic assay
Species: mouse **Sex:** male
Strain: C3H
Route of admin.: i.p.
Exposure period: 21 days
Doses: 250 mg/kg/d
Result: negative

Method: other: no data
Year: 1967
GLP: no
Test substance: other TS

Remark: Chromosomal aberration test in C3H mouse testes.
Test substance: caffeine
Reliability: (3) invalid
only one dose tested
07-DEC-2001 (212)

Type: Cytogenetic assay
Species: rat **Sex:**
Route of admin.: i.v.
Result: positive

Method: other: no data
Year: 1980
GLP: no data
Test substance: other TS

Remark: Rat Guérin ascites tumor cells were examined.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature, tumor cells
07-DEC-2001 (213)

Type: Cytogenetic assay
Species: other: Chinese hamster, mouse **Sex:**
Route of admin.: i.p.
Doses: no data
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: no data

Remark: Chinese hamster and BALB/c mouse bone marrow was scored; positive and negative results were observed.
Test substance: caffeine
Reliability: (4) not assignable

secondary literature
07-DEC-2001 (214)

Type: Cytogenetic assay
Species: mouse **Sex:**
Strain: other: see remark
Route of admin.: drinking water
Exposure period: see remark
Result: negative

Method: other: no data
Year: 1969
GLP: no
Test substance: other TS

Remark: - C3H mouse meiotic metaphase spermatogenesis after an application period of 351 days;
- male JU mouse after an application period of 90 days
Test substance: caffeine
Reliability: (4) not assignable
Original reference not yet available
07-DEC-2001 (215) (216)

Type: Cytogenetic assay
Species: mouse **Sex:**
Route of admin.: drinking water
Exposure period: 1 day
Result: negative

Method: other: no data
Year: 1967
GLP: no
Test substance: other TS

Remark: Mouse ascites S2-sarcoma cells were injected to mice. Chromosomal aberration were studied at ascites cells.
Test substance: caffeine
Reliability: (4) not assignable
Original reference not yet available
07-DEC-2001 (217)

Type: Cytogenetic assay
Species: human **Sex:**
Route of admin.: other: Caffeine tablets
Exposure period: 4 weeks
Doses: 800 mg/daily (4x200 mg)
Result: negative

Method: other: no data
Year: 1972
GLP: no
Test substance: other TS

Remark: Lymphocytes in culture from 9 human volunteers on a regimen of 800 mg/kg/day (4 x 200 mg) for 4 weeks manifested no

significant increase in chromosome damage. The highest level of caffein in the plasma was 30 ug/ml. Multiple exposures of lymphocyte cultures from other untreated donors to this concentration (30 ug/ml) was also without chromosome-damaging effect. However, single exposure of cells at the 48h time of culture produced damage (gaps and breaks only, no exchanges) in the 250- 750 ug/ml range. These findings were the result of experiments with the lymphocytes from the same four individuals tested on three separate occasions.

Earlier additions at concentrations below 250 ug/ml produced no significant breakeage.
Test condition: 9 volunteers, 25-50 methaphases were analysed per culture, the aberrations examined were only breaks and gaps.
Test substance: caffeine, tablets "Vivarin" 200 mg
Reliability: (2) valid with restrictions
evaluation of chromosomal aberration not to the new standard
Flag: Critical study for SIDS endpoint
17-JUL-2001 (146)

Type: Cytogenetic assay
Species: rat **Sex:** no data
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 117 weeks
Doses: ca. 46 mg/kg/d (0.102% in the diet)
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Result: Thirty rats were fed a diet containing the test substance at a concentration of 0.102% (ca. 46 mg/kg/d); thirty control rats were fed unsupplemented diet. The rats were sacrificed when moribund or after 117 weeks of feeding. Blood was collected by heart puncture and assayed for chromosomal aberrations (gaps, breaks, and structural chromosome changes). No significant difference in the frequency of chromosomal aberrations between treated and control rats was found.
Test condition: Groups of 30 rats.
Test substance: caffeine
Reliability: (2) valid with restrictions
acceptable, well documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
11-SEP-2000 (218)

Type: Cytogenetic assay
Species: mouse **Sex:** male
Strain: C3H
Route of admin.: i.p.
Exposure period: single dose
Doses: 0, 200 mg/kg
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Result: Fourteen male mice were administered the test substance at the maximum tolerated dose, control animals received the vehicle (0.9% saline). After sacrifice, testicular tissues were prepared. Meiotic chromosomes at metaphase I

(diakinesis) were evaluated by phase contrast microscopy for breaks, translocations, and univalent chromosomes. No unusual chromosome changes were seen.

Test condition: Groups of male rats; test group: 14 animals; vehicle control group: no data on number of animals.
Test substance: caffeine
Reliability: (2) valid with restrictions
acceptable, well documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
11-SEP-2000 (219)

Type: Cytogenetic assay
Species: mouse **Sex:** male
Strain: Balb/c
Route of admin.: i.p.
Exposure period: 6 hours
Doses: 50, 100, 150 mg/kg
Result: ambiguous

Method: other: no data
Year: 1981
GLP: no data
Test substance: other TS

Result: These results were the positive control part of a clastogenicity study.
Groups of 3 male Balb/c male mice were given a single i.p. injection of the test substance at dose levels of 50, 100, and 150 mg/kg; 9 mice were injected with the vehicle and were sacrificed at 6 hours after injection with the test substance. A total of 200 well-spread metaphases from each mouse were analysed. Caffeine significantly increased the number of total chromosomal aberrations; however, this was not dose-related. The number of abnormal metaphases per 100 cells was 0.61, 1.50, 6.33, and 3.66 in the groups administered 0, 50, 100 and 150 mg/kg, respectively. Chromosomal aberrations included gaps and breaks; chromatid exchanges and centric fusions were not observed.
Test substance: caffeine
Reliability: (3) invalid
animals were killed 6h after treatment, no longer incubation time, only 3 animals were used. Significant methodological deficiencies.
17-DEC-2001 (220)

Type: Cytogenetic assay
Species: mouse **Sex:** female
Strain: C57BL
Route of admin.: drinking water
Exposure period: up to 5 days
Doses: ca. 2000 mg/kg/d (1% in the drinking water)
Result: negative

Method: other: no data
Year: 1975
GLP: no
Test substance: other TS

Remark: The primary objective of this study was to investigate the clastogenic effects of methyl methansulfonate (MMS) and N-methyl-N-nitrosurea (MNNU) in the presence and absence of caffeine.
Result: Groups of 3-4 female C57Bl mice were administered the test substance at a concentration of 1% (w/v) in the drinking water or unsupplemented water for up to 5 days and were sacrificed thereafter. Bone marrow cells were prepared from the femurs and tibiae; 50 or more consecutive well-spread meatphases from each mouse were scored. The test substance did not significantly alter the number of chromosomal aberrations.
Test substance: caffeine
Reliability: (3) invalid
significant methodical deficiencies
07-DEC-2001 (221)

Type: Dominant lethal assay
Species: other: silkworm **Sex:** male
Route of admin.: other: injection
Doses: 0.1 - 100 ug/pupa
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Result: No dominant lethality was observed in sperm of the silkworm (Bombyx mori) after treatment of mid-pupae with the test substance with (presumably single) doses ranging from 0.1 to 100 ug/pupa.
Only abstract available; no further data.
Test substance: caffeine
15-MAY-2001 (222)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: other: C3H, 101 x C3H, C57Bl
Route of admin.: drinking water
Exposure period: 245 - 550 days
Result: negative

Method: other: no data
Year: 1972
GLP: no
Test substance: other TS

Remark: Treatment periods:
- C3H and 101 x C3H mice for 550 days;
- C3H mice for 351 days;
- 101 x C3H mice for 246 days;
- C57Bl mice for 245 days.

Test substance: caffeine
Reliability: (4) not assignable

original reference not yet available

07-DEC-2001 (223)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: CD-1
Route of admin.: drinking water
Exposure period: 8 weeks
Doses: 3.6, 13.4, 49, 122 mg/kg/d (20, 60, 200, 600 ppm in the drinking water)

Result: negative

Method: other: no data
Year: 1973
GLP: no
Test substance: other TS

Result: Groups of 6 male mice were administered the test substance in the drinking water at concentrations of 0, 0.02, 0.06, 0.2 and 0.6 mg/ml) for 8 weeks. Daily consumption of the test substance averaged 0 (untreated control), 3.6, 13.4, 49, and 122 mg/kg bw. Subsequent mating of each male to five females per week for 8 weeks showed no significant increase in dominant-lethal mutations (embryonic deaths) whether expressed as early deaths per pregnant female or as mutation index. Although males of the two highest dose groups produced
fewer pregnancies, litter sizes of females giving birth were not reduced. Litter sizes showed no significant preimplantation losses.
Test substance: caffeine
Reliability: (2) valid with restrictions
07-DEC-2001 (224)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: other: 101 x C3H
Route of admin.: i.p.
Exposure period: single dose
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
original reference not yet available
07-DEC-2001 (223)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: other: C3H, 101 x C3H, C57Bl
Route of admin.: other: see remark
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Remark: Route of administration:
- C3H mice i.p.;
- 101 X C3H mice via drinking water;
- C57Bl mice unspecified oral application

Test substance: caffeine
Reliability: (4) not assignable
original reference not yet available
07-DEC-2001 (225) (226)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: ICR
Route of admin.: other: drinking water or i.p.
Exposure period: see remark
Doses: see remark
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Remark: ICR/Ha Swiss mice were applied the test substance either via the drinking water (0.1%; ca. 200 mg/kg/d) for 8 weeks prior to mating or as a single i.p. injection at dose levels in the range between 168 - 240 mg/kg.
Test substance: caffeine
Reliability: (3) invalid
significant methodicological deficiencies
07-DEC-2001 (227)

Type: Dominant lethal assay
Species: mouse **Sex:**
Strain: other: CD
Route of admin.: oral unspecified
Exposure period: 3, 6 weeks
Doses: 90 mg/kg (6 weeks), 112 mg/kg (3 weeks)
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Test substance: caffeine
Reliability: (4) not assignable
ORIGINAL REFERENCE NOT YET AVAILABLE
07-DEC-2001 (117)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: CD-1
Route of admin.: other: drinking water or gavage
Exposure period: 8 weeks (drinking water) or 5 days (gavage)
Doses: ca. 112 mg/kg/d (drinking water) or 90 mg/kg/d (gavage)
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Result: The dominant lethal effect of the test substance was studied in SPF Swiss CD-1 mice. Groups of 50 male mice were administered the test substance (in tap water) by gavage at doses of 0 (vehicle control) or 90 mg/kg/d daily for 5

consecutive days. Ten male mice were administered a single i.p. dose of 0.125 mg/kg of trenimon (positive control). Hundred and fifty males were administered the test substance in the drinking water for 8 weeks; the average daily dose was 112 mg/kg.
Controls (150 males) were given unsupplemented tap water. At the first and third week after the treatment periods, each male (treated or untreated) was mated with 2 untreated females. No mutagenic induction of dominant lethals, preimplantation losses or depression of female fertility attributable to the test substance was observed.

Test condition: Groups of 50 male mice; control group: 150 male mice.
Test substance: caffeine
Reliability: (2) valid with restrictions
acceptable, well documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint

11-SEP-2000 (228)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: CD-1
Route of admin.: i.p.
Exposure period: single dose
Doses: 15 mg/kg
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Result: Five male mice were given a single i.p. injection of 15 mg/kg of the test substance; five control mice remained untreated. Each male was mated to five females weekly for 7 weeks. Embryonic deaths did not show any effect of the test substance. Litter sizes showed no significant preimplantation losses.
Test substance: caffeine
Reliability: (3) invalid
07-DEC-2001 (224)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: CD-1
Route of admin.: drinking water
Exposure period: 16 weeks
Doses: 4, 13 mg/kg/d (20, 60 ppm in the drinking water)
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Result: Groups of 5 male mice were administered the test substance

in the drinking water at concentrations of 0 (untreated control), 0.02, and 0.06 mg/ml) for 16 weeks. Daily consumption of the test substance averaged 0, 4, and 13 mg/kg bw. Each male was mated to five females per week for 7 weeks. Fertility and litter size were not affected by treatment with the test substance; no substance-related induction of dominant-lethal mutation was noted. Litter sizes showed no significant preimplantation losses.

Test substance: caffeine
Reliability: (3) invalid
07-DEC-2001 (224)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: C57BL
Route of admin.: drinking water
Exposure period: 100 or 140 days
Doses: ca. 50, 100, 200, 400, 600, 800, 1000 mg/kg/d (0.025, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5% in the drinking water)
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Result: Male C57Bl mice were administered the test substance in the drinking water for 100 days (0.025, 0.05, 0.1, 0.2, 0.3, 0.5%) of for 140 days (0.2 and 0.4%) and were then mated to untreated C3H females for three weeks or more. According to the authors, preliminary results showed that the test substance induced dominant-lethal mutations as indicated by preimplantation losses and resorptions. However, the data were considered to be not sufficient to establish a good dose-relationship.

Test substance: caffeine
Reliability: (3) invalid
inconsistent results
07-DEC-2001 (229)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Route of admin.: i.p.
Exposure period: 42 days
Result: negative

GLP: no
Test substance: no data

Test substance: caffeine
Reliability: (4) not assignable
original reference not yet available
07-DEC-2001 (230)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** male/female

Strain: other: Canton-S
Route of admin.: other: i.p. and oral feed
Exposure period: see freetext
Doses: ca. 1940 ug/ml (0.01 M)
Result: negative

Method: other: Mueller-5
GLP: no
Test substance: other TS

Method: For the detection of sex-linked recessive lethals, the Muller-5 method was used (brood interval of 48 hours, each male being mated to 3 Muller females). The test substance was administered by 3 different methods:

- injection of 0.1 ul of a 10 mM solution in 0.7% saline into
  24-hour adult males
- allowing newly-emerged adult males to feed on 10 mM caffeine plus 10% sucrose solution for 72 hours
- larvae were reared on unyeasted culture medium containing 10 mM of caffeine.

A total of 7 broods was collected in each experiment, extending over a period of 14 days.

Result: In all experiments, the number of recessive lethals was not statistically significantly different from the spontaneous mutation rate.

Test substance: caffeine

18-MAY-2001 (231)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** male
Strain: other: Berlin K
Route of admin.: oral feed
Exposure period: 3 days
Doses: up to 971 ug/ml (up to 5 mM)
Result: negative

Method: other: according to Wuergler, F.E. et al. in: Kilbey, B.J. et al. (eds.): Handbook of mutagenicity test procedures, Elsevier, Amsterdam; pp. 335-373
Year: 1977
GLP: no data
Test substance: other TS

Remark: Berlin K males were fed the test substance and mated with untreated Basc females. Sex-linked recessive lethals were scored in the F2 generation and confirmed in the F3 generation.

Test substance: caffeine; according to the authors, purity was of the finest pure grade

30-AUG-2000 (114)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:**
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Positive and negative results were observed (route of administration: oral feed, injection, or via unspecified application).

Test substance: caffeine

30-AUG-2000 (232) (233) (234) (235)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** male
Strain: other: rod X

Route of admin.: oral feed
Exposure period: 24, 48 hours
Doses: nontoxic doses; no further data
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Result: Non-toxic concentrations of the test substance in 10% sucrose were fed to adult rod X males for 24 or 48 hours. The treated males were mated to Oster females; 4 sucessive 3-day broods were analysed to assess the sensitivity of post-meiotic and pre-meiotic germ cells. Sex-chromosome loss and sex-linked recessive lethal mutations were used as endpoints. According to the authors, non-toxic doses of the test substance did not induce any significant increase in the frequency of sex-chromosome loss and sex-linked recessive lethals.
Only abstract available; no further data.
Test substance: caffeine
15-MAY-2001 (236)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:**
Route of admin.: oral feed
Exposure period: 1 hour
Doses: 1% in the diet
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Remark: Induction of somatic damage (and premature aging), chromosome breakage, dominant lethality, sex-linked recessive lethals, X-chromosome loss, and differential mortality (preferentally killing of males) were observed.
Test substance: caffeine
15-MAY-2001 (229) (237)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** male
Strain: other: Canton-S, Oregon-R
Route of admin.: oral feed
Doses: 0.25, 0.5% in the diet
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Remark: Second and third-instar larvae were reared on medium containing the test substance. Treated adult males were mated with untreated Muller-5 females. No substance-related effect was seen.
Test substance: caffeine
25-AUG-2000 (238)

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** male
Strain: other: Canton-S
Route of admin.: i.p.
Doses: 0.5%
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Remark: Adult males were injected with the tests ubstance in saline and were mated with untreated Muller-5 females. No substance-related effect was seen.
Test substance: caffeine
25-AUG-2000 (238)

Type: Heritable translocation assay
Species: Drosophila melanogaster **Sex:**
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Remark: No induction of translocations was observed.
Test substance: caffeine
30-AUG-2000 (239)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: NMRI
Route of admin.: i.p.
Exposure period: 2 times within 24 hours
Doses: up to ca. 97.1 mg/kg (up to 0.5 mmoles/kg)
Result: negative

Method: other: according to Schmid, W. in: Hollaender, A. (ed.): Chemical Mutagens, Vol. 4, Plenum, New York; pp. 31-53
Year: 1976
GLP: no data
Test substance: other TS

Result: Groups of 4 mice were administered the test substance at three different dose levels (two i.p. injections within 24 hours); the highest dose level was 0.5 mmoles/kg (ca. 97.1 mg/kg). Four control mice received the vehicle. Six hours after the second dose, the animals were sacrificed. Bone marrow smears were prepared for the evaluation of micronucleated cells (scoring of 1000 polychromatic erythrocytes for each animal). No statistically significant increase in the frequency of micronucleated erythrocytes was found.
Test condition: Groups of 4 mice.
Test substance: caffeine; according to the authors, purity was of the

highest grade commercially available
Reliability: (2) valid with restrictions
acceptable, well documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
11-SEP-2000 (114)

Type: Micronucleus assay
Species: Chinese hamster **Sex:** no data
Strain: no data
Route of admin.: gavage
Exposure period: 1 or 2 doses
Doses: 0, 45, 75, 100, 300 mg/kg/d
Result: positive

Method: other: according to Schmid, W.: Mutat. Res. 31, 9-15
Year: 1975
GLP: no data
Test substance: other TS

Result: Groups of 8 hamsters were given 1 or 2 gavage doses of the test substance in water at doses of 0 (negative control), 45, 75, 150, and 300 mg/kg or 10 mg/kg endoxan (positive control). The doses were applied at 30 h and 6 h (in the case of double dosing only) prior to sacrifice. Bone marrow was removed from the femur and prepared for analysis. According to the authors, a clear cut induction of micronuclei was seen at the high dose only.
Test substance: caffeine, pure
Reliability: (2) valid with restrictions
07-DEC-2001 (240)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: other: Swiss CD-1 (outbred), MS/Ae (inbred)
Route of admin.: gavage
Exposure period: 1 or 2 doses
Doses: 0, 50, 75, 100 mg/kg/d
Result: ambiguous

Method: other: according to Schmid, W.: Mutat. Res. 31, 9-15
Year: 1975
GLP: no data
Test substance: other TS

Result: According to the authors, a weak induction of micronuclei was seen in both inbred and outbred mice at the high dose only.
Test condition: 4 males and 4 females/ strain were treated. These groups of 8 mice/strain were given 1 or 2 gavage doses of the test substance in water at doses of 0 (negative control),50, 75 and 100 mg/kg or i.p. 5 mg/kg Thio-tepa (positive control). The doses were applied at 30 h and 6 h (in the case of double dosing only) prior to sacrifice. Bone marrow was removed from the femur and prepared for analysis.

2 x 1000 polychromatic erythrocytes were evaluated per animal in 2 different slides.
Test substance: caffeine, pure
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

18-DEC-2000 (240)

Type: Micronucleus assay
Species: mouse **Sex:** no data
Strain: other: C3H x C57
Route of admin.: i.p.
Exposure period: daily for 5 days
Doses: no data
Result: negative

Method: other: no data
GLP: no
Test substance: other TS

Remark: Marrow suspension were prepared and 1000 reticulocytes were examined
Test substance: caffeine
Reliability: (4) not assignable
original reference not yet available

07-DEC-2001 (109)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: CD-1
Route of admin.: i.p.
Doses: 100, 160, 250 mg/kg
Result: negative

Method: other: no data
Year: 1974
GLP: no data
Test substance: other TS

Remark: Bone marrow micronucleus test using mice. The compounds were given twice i.p. with an interval of 24h. No induction of micronuclei were observed.
Test substance: caffeine
Reliability: (2) valid with restrictions
meets generally accepted scientific standards

07-DEC-2001 (241)

Type: Micronucleus assay
Species: other: Chinese hamster, mouse **Sex:**
Route of admin.: oral unspecified
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: other TS

Remark: CBA male mouse, rat bone marrow and peripheral blood and Chinese hamster bone marrow was examined. Positive and nebative results were observed.
Test substance: caffeine
Reliability: (4) not assignable
07-DEC-2001 (242) (243)

Type: Micronucleus assay
Species: mouse **Sex:**
Strain: other: embryos in vitro
Route of admin.: other: in vitro treatment
Doses: 0.1 and 2 mM
Result: ambiguous

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Mouse pre-implantation embryo, ex vivo
Combination study with x-ray, Caffeine alone only the Control group. Slight increase of micronuclei in different time postcoceptionem.
Test substance: caffeine
Reliability: (4) not assignable
original reference not yet available
07-DEC-2001 (244)

Type: Micronucleus assay
Species: human **Sex:**
Route of admin.: unspecified
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Erythrocytes/reticulocytes of a splenectomized human were examined.
Test substance: caffeine
Reliability: (4) not assignable
original reference not yet available
07-DEC-2001 (245)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: C57BL
Route of admin.: s.c.
Exposure period: single or 3 injections
Doses: 50, 100 mg/kg/d
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Male, non-pregnant female and pregnant mice were given single injections of the test substance (pregnants on day 17 of gestation) at dose levels of 50 and 100 mg/kg or 3 daily injections of 100 mg/kg/d for 3 consecutive days (pregnants on days 15 to 17 of gestation). No clastogenic effect was seen in mouse bone marrow or in fetal livers. Untreated controls and positive controls (30 mg/kg cyclophosphamide (i.p.) or 2.0 mg/kg mitomycin C (i.p.)) were included.
Test substance: caffeine
Reliability: (2) valid with restrictions
07-DEC-2001 (246)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: other: BDF1
Route of admin.: s.c.
Exposure period: single or 3 injections
Doses: 50, 100 mg/kg/d

Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Male, non-pregnant female and pregnant mice were given single injections of the test substance (pregnants on day 17 of gestation) at dose levels of 50 and 100 mg/kg or 3 daily injections of 100 mg/kg/d for 3 consecutive days (pregnants on days 15 to 17 of gestation). No clastogenic effect was seen in mouse bone marrow or in fetal livers. Untreated controls and positive controls (30 mg/kg cyclophosphamide (i.p.) or 2.0 mg/kg mitomycin C (i.p.)) were included.
Test substance: caffeine
Reliability: (2) valid with restrictions
07-DEC-2001 (246)

Type: Micronucleus assay
Species: mouse **Sex:** male
Strain: Swiss
Route of admin.: i.p.
Exposure period: 4 days
Doses: 0, 75, 150 mg/kg/d
Result: negative

Method: other: no data
Year: 1990
GLP: no data
Test substance: other TS

Remark: Groups of 8 folate-deficient mice were adminstered the test substance in saline (daily for 4 consecutive days). Bone marrow and peripheral blood was evaluated for micronucleated erythrocytes. A significant and dose-related increase in micronuclei was observed in these mice. Both mature and immature erythrocytes were affected.
No or a nonsignificant increase of micronucleated erythrocytes were observed in normal mice.
The results demonstrated that folate deficiency causes cytogenetic damage in mice and that caffeine act synergistic with folate deficiencies to induce cytogenetic damage in vivo.
Test substance: caffeine
Reliability: (4) not assignable
original reference not yet available
07-DEC-2001 (247)

Type: Mouse spot test
Species: mouse **Sex:** female
Strain: other: other PT and HT mice
Route of admin.: i.p.
Doses: see test conditions
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Result: Combination study with urethan.
Caffeine was not mutagenic, no differences between control and treated groups. No induction of spots in the caffeine-treated group.
Posttreatment with caffeine did not suppress but rather slightly but not significantly increased the incidence of colored spots (p=0.35) and white midventral spots (p=0.1).
Test condition: Examination of effects of caffeine on urethan-induced somatic mutations (combination study).
Pregnant mice received a single s.c. injection of 1.0 mg/g bw of day 11. immediately after treatment with urethan, 5 i.p. injections 0f 0.25umol Caffeine/g bw. were given to pregnant mice at 6 h intervals. One control group was treated only with Caffeine.
Test substance: caffeine
Reliability: (3) invalid
significant methodical deficiencies, caffeine group only the control (4 animals were treated)
19-DEC-2001 (248)

Type: Sister chromatid exchange assay
Species: Chinese hamster **Sex:** no data
Strain: no data
Route of admin.: gavage
Exposure period: single dose
Doses: 0, 45, 75, 150, 300 mg/kg
Result: positive

Method: other: according to Allen, J.W. et al.: Somat. Cell. Genet. 4, 393-406
Year: 1978
GLP: no data
Test substance: other TS

Result: Groups of 8 hamsters were given single gavage doses of the test substance in water at doses of 0 (negative control), 45, 75, 150, and 300 mg/kg or 10 mg/kg endoxan (positive control). BrdU tablets had been implanted at 2 h prior to dosing. Twenty-four hours after implantation (22 h after dosing), the animals were i.p. injected with 0.02 mg of vincristine and were sacrificed 3.5 h later. Bone marrow was removed from the femur and prepared for SCE analysis.
According to the authors, a slight increase in SCE was seen at 150 mg/kg upwards; the increase was statistically significant at the high dose only.
Test substance: caffeine, pure
Reliability: (2) valid with restrictions
07-DEC-2001 (240)

Type: Sister chromatid exchange assay
Species: mouse **Sex:** male/female
Strain: Swiss

Route of admin.: drinking water
Exposure period: 5, 10, 15 days
Doses: ca. 1000 mg/kg/d (0.5% ion the drinking water)
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Groups of 3 mice received the test substance at a concentration of 0.5% in the drinking water for 5, 10 and 15 days and were sacrificed thereafter. Control mice received unsupplemented water for 5 days and were then sacrificed.

BrdU and colchicine were administered by injection at 19 and 2 hours prior to sacrifice, respectively. Bone marrow was expelled from long bones and prepared for SCE analysis; 25 metaphases per animal (75 metaphases per dose group) were scored. In treated mice, the frequency of SCE/cell was increased in a significant and exposure time-related manner.
Test substance: caffeine
Reliability: (3) invalid
3 animals were used only, one concentration only
07-DEC-2001 (249)

Type: Sister chromatid exchange assay
Species: mouse **Sex:** male
Strain: C57BL
Route of admin.: i.v.
Exposure period: single dose
Doses: 50 mg/kg
Result: positive

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Remark: A weakly positive result was reported.
Result: Mice (no data on number of animals) were intravenously infused with 50 mg/kg/h BrdU in phosphate-buffered saline for 26 h and were sacrificed thereafter. One hour after starting the BrdU infusion, the mice were given a single i.v.
dose of 50 mg/kg of the test substance; colcemid was injected i.v. at 2 hours prior to sacrifice. Bone marrow was removed from both femurs; and the bone marrow cells were prepared for SCE analysis. SCE were enumerated in at least 20 second-replication-cycle metaphase cells. According to the authors, the test substance was tested at doses of up to 50 mg/kg (no further details given); above this dose level, cell replication was inhibited to the point where insufficient second-replication-cycle cells could be found for SCE determination.
According to the authors, the test substance was a weak

inducer producing an SCE level slightly greater than baseline SCE level.
Test substance: caffeine
Reliability: (3) invalid
one concentration was tested only, no data about number of animals used
07-DEC-2001 (250)

Type: Sister chromatid exchange assay
Species: Chinese hamster **Sex:** male/female
Route of admin.: i.p.
Exposure period: once
Doses: 100, 200 mg/kg bw
Result: negative

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Remark: Bone marrow was examined., no significant increase in SCE rate
Test substance: Caffeine
caffeine
Reliability: (2) valid with restrictions
meets generally accepted standards
07-DEC-2001 (251)

Type: Sister chromatid exchange assay
Species: Chinese hamster **Sex:**
Route of admin.: gavage
Doses: 0, 30, 75, 150, 225, 300, 450, 600 mg/kg

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Tablet method with BrdU; bone marrow cells were examined. Results only in a graphical manner.
Test substance: caffeine
Reliability: (3) invalid
19-DEC-2001 (252)

Type: Sister chromatid exchange assay
Species: Chinese hamster **Sex:** male/female
Strain: no data
Route of admin.: gavage
Exposure period: 2 doses within 24 hours
Doses: 0, 20, 100, 200, 400 mg/kg
Result: positive

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Remark: Groups of hamsters were administered by gavage an aqueous solution of the test substance at dose levels of 0 (vehicle control), 20, 100, 200, and 400 mg/kg; each dose was administered two times within 24 hours. Positive controls were i.p. injected twice with 5 mg/kg of cyclophosphamide. Solvent control group consisted of 6 hasters/sex; positive control group and 20, 100, and 200 mg/kg/d groups consisted of 4 hamsters/sex; 400 mg/kg/d group consisted of 2 hamsters/sex. Bone marrow smears were prepared for SCE analysis. Six hundred metaphases (vehicle control), 400 metaphases (20, 100, 200 mg/kg/d and positive control), or 200 metaphases (400 mg/kg/d) were scored.
Test substance: caffeine, pure
Reliability: (2) valid with restrictions
meets generally accepted standards
07-DEC-2001 (253)

Type: Sister chromatid exchange assay
Species: rat **Sex:** no data
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 117 weeks
Doses: ca. 46 mg/kg/d (0.102% in the diet)
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Result: Thirty rats were fed a diet containing the test substance at a concentration of 0.102% (ca. 46 mg/kg/d); thirty control rats were fed unsupplemented diet. The rats were sacrificed when moribund or after 117 weeks of feeding. Blood was collected by heart puncture and assayed for sister chromatid exchanges. According to the authors, the frequency of sister chromatid exchanges was similar in treated and control rats.
Test condition: Groups of 30 rats.
Test substance: caffeine
Reliability: (2) valid with restrictions
acceptable publication which meets basic scientific principles
11-SEP-2000 (218)

Type: Somatic mutation assay
Species: Drosophila melanogaster **Sex:**
Route of admin.: oral feed
Exposure period: 48 or 72 hours
Doses: 0.3% in the diet for 72 h; 0.5% in the diet for 48 h
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Wing spot test; induction of somatic mutation and recombination was observed.
Test substance: caffeine, pure
15-MAY-2001 (254)

Type: Unscheduled DNA synthesis
Species: rat **Sex:** male
Strain: Fischer 344
Route of admin.: oral unspecified
Exposure period: single dose
Doses: up to 1000 mg/kg
Result: negative

Method: other: no data
GLP: no data
Test substance: other TS

Remark: UDS was measured in pancreatic cells obtained from treated rats.
Test substance: caffeine
Reliability: (4) not assignable
abstract
07-DEC-2001 (255)

Type: other: Comparative cytogenetic studies: micronucleus, chromosome aberration, SCE
Species: other: mouse, Chinese hamster **Sex:** male/female
Strain: other: CD-1; Chinese hamster
Route of admin.: i.p.
Exposure period: twice inert 24h
Doses: 100, 200, 250 mg/kg bw
Result: negative

Method: other: According Schmid 1975; Tsuchimoto and Matter 1977
Year: 1979
GLP: no
Test substance: other TS

Remark: Comparative cytogenetic studies of bone marrow cells of mice and Chinese hamster.
The animals received two applications of Caffeine for MNT and CA, while those for the SCE received a single treatment.
Micronucleus test mice:
The substance was administered twice with an interval of 24h, 2 mice of each sex were used per dose level. Six hours after the second application, the mice were killed. 1000 erythrocytes (including PCE and NCE) were examined for the presence of micronuclei.
Micronucleus test and chromosome analysis Chinese hamster:
The MNT and CA were made using the same animals. Caffeine was administered twice with an interval of 24h, 3 animals per dose level were tested. 6h after the second application the animals were killed. 1000 erythrocytes and 50 metaphases were examined per animal.
SCE in Chinese hamster:

Two animals/sex were tested per dose level, 50 metaphases were analysed per animal. The hamsters were treated i.p with FUDR and BUDR simultanously 0,2,3,4,5,6,7,8 h, the test substance 2h after the first FUDR injection. Colchicine i.p. 24h after the first FUDR administration. Two hours later the animals were killed and the chromosome preparations were made.

Result: Caffeine did not show positive findings with any of the three methods used. A slight and insignificant incresde in chromosome aberrations at 200 mg/kg was considered an indirect effect of an extremly high dosage.

Test substance: Caffeine (Sandoz), dissolved in 0.9% sodiumchloride -solution

Reliability: (2) valid with restrictions
comparable to guideline studies with acceptable restriction

Flag: Critical study for SIDS endpoint

20-JUL-2001 (256)

Type: other: DNA damage
Species: mouse **Sex:** male
Strain: Swiss
Route of admin.: i.p.
Doses: 100 mg/kg
Result: positive

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Single strand DNA breaks (alkaline elution) were seen in tissues of liver and kidney.
Test substance: caffeine

Reliability: (4) not assignable
original reference not yet available
07-DEC-2001 (257)

Type: other: aneuploidy test
Species: Drosophila melanogaster **Sex:**
Result: ambiguous

Method: other: no data
GLP: no
Test substance: other TS

Remark: Induction (positive result) and no induction (negative result) of aneuploidy was reported.
Test substance: caffeine
15-MAY-2001 (258) (239) (259) (260)

Type: other: aneuploidy test
Species: Drosophila melanogaster **Sex:** female
Strain: no data
Route of admin.: oral feed
Exposure period: 1 hour
Doses: 1% in the diet
Result: positive

Method: other: no data
GLP: no
Test substance: other TS

Result: Female larvae were eposed to the test substance (1% in the diet) for 1 hour, returned to normal millieu and were allowed to hatch. A significant change in the sex ratio (% of males in the total number of flies) was observed; sex ratio was 47.1 and 52.6% males in the dosed and untreated control group, respectively.
Test substance: caffeine
18-MAY-2001 (229)

Type: other: chromosome loss and non-disjunction
Species: Drosophila melanogaster **Sex:** male
Strain: other
Route of admin.: other: i.p. and oral feed
Exposure period: see freetext
Doses: ca. 1940 ug/ml (0.01 M)
Result: positive

Method: other
GLP: no
Test substance: other TS

Method: Non-disjunction and chromosome loss in either parent were estimated by crossing females with rod-X males or ring-X males. Brood intervals were 72 hours of 48 hours. The test substance was administered by 3 different methods:
- injection of 0.1 ul of a 10 mM solution in 0.7% saline

into 24-hour adult males
- allowing newly-emerged adult males to feed on 10 mM caffeine plus 10% sucrose solution for 72 hours
- larvae were reared on unyeasted culture medium containing 10 mM of caffeine.

Result: In the larvae, increased frequencies of chromosome loss was observed in both males and females (10- and 5- fold of control respectively). There was some evidence that treatment with the test substance can lower the frequency of non-disjunction, at least in males.
No significant effect of the test substance on chromosome loss and non-disjunction was observed in adults.

Test substance: benzophenone-2 (2,2',4,4'-tetrahydroxybenzophenone); no data on purity of the compound

18-MAY-2001 (231)

Type: other: host-mediated assay
Species: mouse **Sex:** female
Strain: NMRI
Route of admin.: i.p.
Exposure period: 3 hours
Doses: 2 x 91 mg/kg (2 x 0.5 mmol/kg)
Result: negative

Method: other: according to Mohn and Ellenberger in: Kilbey, B.J. et al. (eds.): Handbook of mutagenicity test procedures, Elsevier, Amsterdam; pp. 95-118
Year: 1977
GLP: no data
Test substance: other TS

Remark: Host mediated assay with Escherichia coli K12 (343/113). Mice were i.v. injected with the bacteria and were then given two i.p. injections of the test substance 2 x 0.5 mmol/kg = 2 x 91 mg/kg). After 3 hours, the mice were sacrificed; livers were prepared for the bacterial mutagenicity assay.

Test substance: caffeine; according to the authors, purity was of the finest pure grade

Reliability: (2) valid with restrictions
meets general accpted scientific standards

Flag: Critical study for SIDS endpoint

07-DEC-2001 (114)

Type: other: host-mediated assay
Species: mouse **Sex:** no data
Strain: Swiss
Route of admin.: i.m.
Doses: up to 10 mg/ml
Result: negative

Method: other: no data
Year: 1969
GLP: no
Test substance: other TS

Remark: Host mediated microbial assay in Swiss albino mice receiving i.p. injection of Salmonella typhimurium and i.m. injection of caffeine. The highest concentration tested was 1000 µg/0.1 ml (= 10 mg/ml).
Test substance: caffeine
Reliability: (3) invalid
results in a table only, no further data

19-DEC-2001 (261)

Type: other: meiotic crossing over
Species: Drosophila melanogaster **Sex:**
Result: ambiguous

Method: other: no data
GLP: no
Test substance: other TS

Remark: Induction of meiotic crossing over was seen in oogonia (positive), but not in oocytes and stem cells (negative).
Test substance: caffeine

30-AUG-2000 (262)

Type: other: specific locus test
Species: mouse **Sex:** male/female
Strain: other: (C3H/HCH female x 101/H male) F1 female x CDT male
Route of admin.: drinking water
Exposure period: 70 days
Doses: up to ca. 12000 mg/kg/d
Result: negative

Method: other: no data
Year: 1962
GLP: no
Test substance: other TS

Remark: Mouse specific locus test.
The test substance was tested up to the maximum tolerated dose (12000 mg/kg); this dose level was the higest ineffctive dose in this assay.
Test substance: caffeine
Reliability: (3) invalid

07-DEC-2001 (263)

Type: other: test on abnormal sperm
Species: mouse **Sex:** male
Strain: other: C3H x C57
Route of admin.: i.p.
Exposure period: daily for 5 days
Doses: no data
Result: negative

Method: other: no data
GLP: no

Test substance: other TS

Remark: Sperm abnormality assay; after 35 days sperm-cell suspension were prepared and 1000 sperms were examined
Test substance: caffeine
Reliability: (3) invalid
07-DEC-2001 (109)

5.7 Carcinogenicity

Species: rat **Sex:** male/female
Strain: Wistar
Route of administration: drinking water
Exposure period: 78 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: 26 weeks
Doses: ca. 90, 180 mg/kg/d (0.1%, 0.2% in the drinking water)
Control Group: yes, concurrent no treatment

Method: other: no data
Year: 1982
GLP: no data
Test substance: other TS

Result: Groups of 50 rats/sex were given the test substance at concentrations of 0% (control), 0.1%, and 0.2% in the drinking water for 78 weeks and were sacrificed in week 104. According to the authors, the total doses per animal amounted 14.5 g (low dose males), 13.9 g (low dose females), 26.6 g (high dose males), and 21.7 g (high dose females). Observations included mortality, body weight, water intake and postmorten and histological examination. Various tumors were found in both treated and control group; however, tumor incidence was similar in all groups. There was no evidence of carcinogencity of the test substance in rats.
Test substance: synthetic caffeine; according to the authors, purity was 100%
Reliability: (4) not assignable
secondary literature
17-DEC-2001 (264) (265) (266)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: drinking water
Exposure period: 104 weeks
Frequency of treatment: continuously in the diet
Post exposure period: no data
Doses: 12, 26, 49, 102 mg/kg/d (males); 15, 37, 80, 170 mg/kg/d (females) (200, 430, 930, 2000 ppm in the drinking water)
Result: negative
Control Group: yes, concurrent no treatment

Method: other: no data

Year: 1982
GLP: no data
Test substance: other TS

Result: Groups of 50 animals per sex were administered drinking water containing the test substance at concentrations of 200, 430, 930, and 2000 mg/l (ppm). According to the authors, mean daily intake of the test substance was 12, 26, 49, and 102 mg/kg in males and 15, 37, 80, and 170 mg/kg in females. Two control groups, each of 50 animals per sex were given unsupplemented water.
There was a slightly increased mortality in males at 2000 mg/l. Decreased body weights were found in both sexes at higher dose levels.
There were no statistically significant differences between control and treated animals for tumors of any type except for mammary fibroadenomas, the incidence of which was 50% in the controls compared with 26% in the highest-dose group. The incidence of mammary fibroadenomas showed a significant inverse dose-response relationship.
In conclusion: There was no statistically significant increase in tumor incidence in treated animals as compared to controls even at doses exceeding the maximum tolerated dose and given to animals over major portion of their lifespan.
Test substance: food grade natural caffeine (containing less than 0.01% theobromine)
Reliability: (2) valid with restrictions
comparable to guideline studies
Flag: Critical study for SIDS endpoint
17-DEC-2001 (267)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: drinking water
Exposure period: 12 months
Frequency of treatment: continuously in the drinking water
Post exposure period: no data
Doses: ca. 180 mg/kg/d (2000 ppm in the drinking water)
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: other TS

Result: Rats were administered drinking water containing the test substance at a concentration of 2000 mg/l (ppm). According to the authors, total dose amounted ca. 13.5 g/animal. Control rats were given unsupplemented water. Histopathology was limited to the pituitary gland. An increased number of pituitary adenomas was observed in the treated group. According to IARC, the study was judged to be of limited value due to short duration, only one sex (males) used, limited histopathology, and that 10 controls were not evaluated because of premature death.
Test substance: caffeine

Reliability: (4) not assignable
seconary literature
17-DEC-2001 (268)

Species: rat **Sex:** male
Strain: Wistar
Route of administration: drinking water
Exposure period: 32 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 280 mg/kg/d (0.25% in the drinking water)
Control Group: yes

Method: other: no data
Year: 1995
GLP: no data
Test substance: other TS

Remark: initiation/promotion study
Result: The aim of the study was to evaluate the effects of the test substance on glandular stomach carcinogenesis induced in rats by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and sodium chloride (NaCl). Four groups of 30 5-week old rats were given 100 ppm MNNG in the drinking water (ca. 11 mg/kg/d) and simultaneously fed a diet containing 5% NaCl (ca. 5550 mg/kg/d) for 8 weeks (initiation phase). Thereafter, the four groups were treated for 32 weeks as follows (promotion phase):
group 1: 0.25% caffeine in the drinking water (ca. 280 mg/kg/d), 5% NaCl in the diet
group 2: tap water, 5% NaCl in the diet
group 3: 0.25% caffeine in the drinking water, unsupplemented diet
group 4: no treatment (tap water, unsupplemented diet)
After termination of the post-initiation phase (at study week 40), all surviving rats were sacrificed; and their stomachs were examined.
Both caffeine and NaCl treatment resulted in growth retardation. Body weight suppression was stronger with caffeine than with NaCl; group-1 rats showed the lowest body weights. The incidences of adenocarcinomas in the pylorus and of atypical hyperplasia in the fundus were significantly decreased in group 1 compared with group 2; however, in both cases the incidences were significantly higher than in group 4 (control). These findings were in good agreement with short-term assay results whereby lipid peroxidation in the glandular stomach mucosa induced by NaCl ingestion was partially inhibited by co-administration of the test substance. In group 3, intake of the test substance alone did not modulate glandular stomach tumor development. According to the authors, these results suggested that the test substance inhibited gastric tumor promotion activity of sodium chloride in rats.
Test substance: caffeine; according to the authors, purity was 98.5%
17-DEC-2001 (269)

Species: rat **Sex:** male
Strain: Fischer 344
Route of administration: drinking water
Exposure period: 6 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 90 mg/kg/d (1000 ppm in the drinking water)
Control Group: yes, concurrent no treatment

Method: other: screening assay
Year: 1988
GLP: no data
Test substance: other TS

Result: The hepatocarcinogenic potential of 112 compounds including the test substance was evaluated in a screening assay using groups of 12-20 rats. The rats were given a single i.p. injection of 200 mg/kg diethylnitrosamine (DEN) and were 2/3 partially hepatectomized 3 weeks later. Treatment with the test substance was begun 2 weeks after DEN injection. After 6 weeks of administration of the test substance (i.e. 8 weeks after DEN injection), the rats were sacrificed. Carcinogenic potential was scored by comparing the number and area of glutathione-S-transferase placental form positive (GST-P+) foci in the liver of treated rats with those of controls given DEN alone. No increase in the number and area of GST-P+-foci was seen in caffeine-treated animals.
Test substance: caffeine
Reliability: (3) invalid
only one dose tested, initiation/promotion test
17-DEC-2001 (270)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: drinking water
Exposure period: 21 months
Frequency of treatment: continuously in the drinkng water
Post exposure period: none
Doses: 110 mg/kg/d
Control Group: yes

Method: other: no data
GLP: no data
Test substance: other TS

Result: The effect of the test substance and phenacetin on N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN)-initiated urothelial carcinogenesis was studied in groups of 50 rats. The rats were given 100 mg/kg BBN and were then administered the test substance (110 mg/kg/d) in the drinking water for 21 months, either alone or in combination with 500 mg/kg/d of phenacetin in the diet. The test substance alone revealed no complete initiating carcinogenic potential for the resting as well as the regenerating bladder urothelium

stimulated to proliferate by a partial cystectomy or cyclophospamide. No cocarcinogenic and/or promoting activity of the test substance on BBN-initiated bladder tumor development was observed. In contrast, increased tumor incidences were seen in rats given the test substance in combination with phenacetin; this increase was greater than an increase observed in rats given phenacetin alone.

Test substance: caffeine

Reliability: (3) invalid
only one dose tested, initiation/promotion test

17-DEC-2001 (271)

Species: mouse **Sex:** female
Strain: other: C3H, BD2F, BALB/c
Route of administration: drinking water
Exposure period: 43 weeks
Frequency of treatment: continuously in the drinking water
Post exposure period: no data
Doses: ca. 50, 100 mg/kg/d (250, 500 mg/l = 250, 500 ppm in the drinking water)
Control Group: yes, concurrent no treatment

Method: other: no data
Year: 1988
GLP: no data
Test substance: other TS

Remark: Histopathology was limited to mammary gland.
initiation/promotion study

Result: The effect of the test substance on carcinomatous and normal mammary gland development was studied in BD2F mice (54-55/group), C3H mice (37-43/group), and BALB/c mice (20/group).

BD2F mice were administered the test substance in the drinking water starting 1 week after a series of 6 weekly 7,12-dimethylbenz(a)anthracene (DMBA) injection. C3H mice were administered the test substance without any pretreatment. In both strains, administration of the test substance (low and high dose) resulted in an increse in mammary carcinoma multiplicity (by 20 and 40%, respectively, in BD2F mice and by 13 and 117%, respectively, in C3H mice). In contrast, the incidence of mammary carcinomas (i.e. the percentage of mice bearing mammary tumors) and mean time to tumor appearance as well as body weight gain were not affected. An increase of mammary adenocarcinomas per animal was noted.

In a second series of studies, the effect of the test substance on mammary gland development in BALB/c mice was assessed in vivo (0, 500 mg/l in the drinking water) and in vitro (organ culture). In treated mice, mammary gland development was significantly increased. In the organ cultures, mammary glands derived from treated mice were more responsive in vitro to a mammotropic hormonal developmental growth stimulus than were mammae derived from untreated

mice.

According to the authors, these results suggested that caffeine consumption enhanced mammary tumorigenesis in C3H and carcinogen-treated BD2F mice and enhanced developmental growth of normal BALB/c mouse mammary gland.

Test substance: caffeine
Reliability: (2) valid with restrictions
17-DEC-2001 (272) (273)

Species: mouse **Sex:** female
Strain: other: C3H/He, GR/A, SHN, SLN
Route of administration: drinking water
Exposure period: 20 to 130 days
Frequency of treatment: continuously in the drinking water
Post exposure period: none
Doses: ca. 100 mg/kg/d (0.05% in the drinking water)
Control Group: yes, concurrent no treatment

Method: other: no data
Year: 1987
GLP: no data
Test substance: other TS

Remark: initiation/promotion study
Result: The formation of precancerous mammary hyperplastic alveolar nodules (HAN) was studied in four strains of mice with varying mammary tumor potentials. Beginning at 21 days of age at weaning, the mice were administered tap water containing 0 or 0.05% of the test substance and were sacrificed at days 40, 60, 90, 120, and 150 days of age. HAN appeared at 90, 60, 60, and 120 days in C3H/He, GR/A, SHN, and SLN mice, respectively. The difference from controls in the number of HAN was statistically significant in the C3H/He mice only. The onset of time of HAN was associated with mammary tumor potential of virgin mice.

The test substance did not affect estrous cycle, plasma levels of prolactin and growth hormones, or endocrine organ weights. According to the authors, these results suggsted that promotion by caffeine of HAN growth was minimally mediated by the endocrine system.

Test substance: caffeine
Reliability: (4) not assignable
secondary literature

17-DEC-2001 (274)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: life-time
Frequency of treatment: 5 d/w
Post exposure period: no data
Doses: 100 mg/kg/d
Control Group: yes, concurrent vehicle

Method: other: no data
Year: 1981
GLP: no data
Test substance: other TS

Result: The rats were administered the test substance at doses of 0 and 100 mg/kg. Reduced mean survival time were recroded for treated rats.
According to IARC, the study was judged to be of limited value.

Test substance: caffeine
Reliability: (4) not assignable
secondary literature

17-DEC-2001 (275)

Species: rat **Sex:** male
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: 117 weeks
Frequency of treatment: daily
Post exposure period: no data
Doses: ca. 46 mg/kg/d (0.102% in the diet)
Control Group: yes, concurrent no treatment

Method: other: no data
Year: 1981
GLP: no data
Test substance: other TS

Result: The rats were fed a diet containing the test substance at concentrations of 0% (control) or 0.102%. Reduced mean survival time was observed in treated animals.
According to IARC, the study was judged to be of limited value due to the use of only one sex (male) and high mortality in treated animals.

Test substance: caffeine; according to the authors, purity was 99.6-99.9%

Reliability: (4) not assignable
secondary literature
17-DEC-2001 (276)

5.8.1 Toxicity to Fertility

Type: Fertility
Species: rat
Sex: male
Strain: other: Osborne-Mendel, Holtzman
Route of administration: oral feed
Exposure Period: up to 75 weeks
Frequency of treatment: continuously in the diet
Doses: ca. 60, 300 mg/kg/d (0.1, 0.5% in the diet)
Control Group: no data specified

Method: other: no data
Year: 1979
GLP: no data
Test substance: other TS

Result: The rats were fed a diet containing the test substance at a concentration of containing 0.5% of the test substance for 64 and 14 to 75 weeks. Testicular atrophy and aspermatogenesis were observed in both experiments. (64 weeks: 13/13 animals had athrophy of testes and aspermatogenesis, 14 weeks: 4/5 animals had atrophie and 3/5 oligospermatogenesis and 1/5 aspermatogenesis; 75 weeks: 8/8 had athrophy, 378 oligospermatogenesis and 5/8 aspermatogenesis)
In a third experiment caffeine were fed to Holzman rats for 19 weeks to determine whether testicular athrophy would be induced in a second strain of rat. The effects were similar to those in the other experiments (11/11 rats had athrophy, 1/11 oligospermatogenesis and 10/11 aspermatogenesis).
Test substance: caffeine
Reliability: (3) invalid
high mortality, small group size, one dose tested only
17-DEC-2001 (277)

Type: Fertility
Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure Period: 23 weeks (during Task 2); for further details see freetext
Frequency of treatment: no data
Premating Exposure Period
male: 1 week (Task 2)
female: 1 week (Task 2)
Duration of test: 36 weeks (Tasks 1, 2, 3, 4)
Doses: 12.5, 25, 50 mg/kg/d
Control Group: yes, concurrent vehicle
NOAEL Parental: < 12.5 mg/kg bw
NOAEL F1 Offspring: < 12.5 mg/kg bw

Method: other: NTP Reproductive Assessment by Continuous Breeding

	(RACB)
Year:	1996
GLP:	yes
Test substance:	other TS

Result: The effects of the test substance on reproduction and fertility of rats was investigated. The test substance was administered in deionized water.

Task 1 (dose finding study; 4-week exposure):
The animals were administered the test substance at doses of 0, 50, 100, 150, or 200 mg/kg/d. According to the authors, based on decreased body weights and food consumption, increased water consumption, and mortality, dose levels of 12.5, 25, and 50 mg/kg/d were selected for the continuous breeding phase.

Task 2 (continuous breeding period; 1-week pre-cohabitation exposure, 16-week cohabitation exposure, 3-week delivery, 3-week weaning):
During 16 weeks of cohabitation, live pup weights were decreased by 7, 7, and 8% in the low, mid and high dose group, respectively. No effects were observed in other reproductive endpoints. One control female and two low dose females died.
According to the authors, the decreased pup weights were concomitant with reduced dam weights. Body weights were significantly lower than control throughout the study (4-7%, 9-15%, and 9-18% in the low, mid and high dose males, respectively, and 5-18%, 5-19%, and 8-19% in low mid, and high dose females, respectively). Food consumption was decreased at the mid and high dose level during the first week (both sexes). At necropsy, no differences were found in the absolute organ weights of F0 males and females. However, many relative organ weights were increased in all treated groups. According to the authors, these increases were attributed to the decreased terminal body weights. No substance-related gross or microscopic lesions were observed in the F0 rats. Percent sperm motility was significantly decreased in high dose F0 males (3%); sperm velocity and average radius was decreased in all treated males (7-12% and 22-36%, respectively). The percent normal sperm was slightly decreased in high dose F0 males. The remaining endpoints of F0 computer-assisted sperm analysis were similar in all groups.

Task 3 (crossover mating, 1-week cohabitation):
No changes in male or female fertility or in pup weights were observed. Reproductive parameters were similar between the dose groups when naive males were mated with control or high dose females and when naive females were mated with control males or high dose males.

Task 4 (second generation evaluation; 8-week maturation phase, 1-week cohabitation):
No mortality was observed in the F1 rats. No substance-related differences in pup weights were found during lactation (post natal days (PND) 1-21). From the initiation of dosing at PND 22 through the maturation phase up to termination of Task 4, mean body weights of the treated males and females were decreased (by ca. 12, 18, and

23% in the low, mid, and high dose group, respectively). Mean body weight and food consumption was decreased (5-19%) in all treated groups.
A decrease in the number of live F2 pups/litter by 21% and in the proportion of pups born alive by 4% was observed in the high dose group. No differences were found in other reproductive endpoints.
Many absolute organ weights were decreased and many relative organ weights were increased in F1 rats (all treated groups). According to the authors, this might be attributed to the decreased body weights. No substance-related gross or microscopic lesions were found in F1 animals. Decreased percent motile sperm (4%) and sperm velocity (9%) was observed in high dose F1 males. The average radius was decreased by 23-36% in mid and high dose F1 males. Other sperm parameters were unaffected.

According to the authors, these results indicated that the test substance was not a selective reproductive toxicant, since the minor effects on sperm motion parameters and on weight/viability of the pups occurred at doses that caused already general toxicity (reduced body weights).
Administration of the test substance to females resulted in fetal toxicity even at the lowest dose level (reduced pup weights at 12.5 mg/kg and more; reduced litter size and viability at 50 mg/kg). Thus, a no-observable-adverse-effect-level (NOAEL) was not established, based on the reduced body weight gain observed in all treated groups.

Test substance: caffeine; according to the authors, purity was 98.6%
Reliability: (1) valid without restriction
guideline study (NTP)
Flag: Critical study for SIDS endpoint
29-JAN-2003 (278)

Type: Fertility
Species: mouse
Sex: male/female
Strain: CD-1
Route of administration: drinking water
Exposure Period: 21 weeks (Task 2)
Frequency of treatment: continuously in the drinking water
Premating Exposure Period
male: 1 week
female: 1 week
Duration of test: 34 weeks (Tasks 1, 2, 4)
Doses: ca. 22, 44, 88 mg/kg/d (0.012, 0.025, 0.05% in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL Parental: 22 mg/kg bw
NOAEL F1 Offspring: 22 mg/kg bw
NOAEL F2 Offspring: 88 mg/kg bw

Method: other: NTP Reproductive Assessment by Continuous Breeding (RACB), according to Reel, J.R. et al.: J. Am. Coll. Toxicol. 4, 147-162

Year: 1985
GLP: no data
Test substance: other TS

Result: Water consumption was not affected by addition of caffeine.

These levels of caffeine, and measured water consumption and body weights, produced calculated consumption estimates nearly equal to 22, 44, and 88 mg/kg/d.

For the F0 animals, there were no effects on body weight. Alopecia occurred in 55% of the medium dose and 50% of the high dose animals. While there were no exposure-related changes in the number of litters/pair, viability, or adjusted
pup weight, the number of live pups per litter, averaged over the 4-5 litters, dropped 15% at the medium dose and 20% for the high dose animals.
No crossover mating trial was conducted, and the offspring from the last litter of control and high dose mice were reared by their dams until weaning, when they were given the same treatment as their parents until mating at 74 ± 10 days of age.

At the second generation mating trial, there were no changes in any reproductive endpoint.

At necropsy, at 0.05% caffeine, male body weight was reduced by 8% while male adjusted liver weight increased by 8%. No change was found in female body or organ weights, or in any sperm endpoint.

In conclusion, a reduction in the number of live pups/litter for the F0 generation was the only reproductive effect observed in this study. This occurred in the absence of a change in body weights in the F0 parental mice.

Test condition: Caffeine was tested simultaneously at two laboratories, each using a variation on the standard RACB study design. This study used Tasks 1, 2, and 4, while the other study in mice utilized Tasks 1, 2, and 3.
Data on body weights, clinical signs, and food and water consumptions were collected during the dose-range-finding phase (Task 1), and used to set exposure concentrations for Task 2 at 0.0, 0.012, 0.025, and 0.05% in drinking water. Water was chosen to mimic the route of human exposure. Groups of 20 animals/sex (Task 2).

Test substance: caffeine; according to the authors, purity was >98.5%

Reliability: (2) valid with restrictions
comparable to guideline study

Flag: Critical study for SIDS endpoint

29-JAN-2003 (279) (280) (281) (282) (283) (284)

Type: Fertility
Species: mouse
Sex: male/female
Strain: CD-1
Route of administration: drinking water
Exposure Period: 21 weeks (Task 2)
Frequency of treatment: continuously in the drinking water
Premating Exposure Period
male: 1 week
female: 1 week

Duration of test: ca. 34 weeks (Task 1,2,3)
Doses: ca. 22, 44, 88 mg/kg/d (0.012, 0.025, 0.05% in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL Parental: 22 mg/kg bw
NOAEL F1 Offspring: 22 mg/kg bw

Method: other: NTP Reproductive Assessment by Continuous Breeding (RACB), according to Reel, J.R. et al.: J. Am. Coll. Toxicol. 4, 147-162
Year: 1985
GLP: yes
Test substance: other TS

Result: Water consumption was not affected by addition of caffeine. These levels of caffeine, and measured water consumption and body weights, produced calculated consumption estimates nearly equal to ca. 22, 44, and 88 mg/kg/d.
Three control, 1 low dose, and 1 middle dose mouse died during the study. Treated mice were also reported to have lost facial hair, but the percentages and groups involved were not specified.

There was no effect on the mean number of litters/pair produced, or on the aggregate mean number of pups/litter (the total number of pups/total number of litters for all pairs at a treatment level). There was a 20% reduction in live male
pups/litter, however. Evaluating each litter individually, after the first litter, the high dose group always delivered 1-2 pups less than the controls; at the fifth litter, the controls delivered a mean of 10.3 ± 7 pups (mean ± SEM), while the high dose group delivered a mean of 8.6 ± 1 pups. The proportion of pups born alive was reduced by 3%, 5%, and 5% in the low, middle and high dose groups, respectively. Additionally, pup body weight adjusted for litter size was reduced by 4% at the high dose.

A crossover mating trial (Task 3) was performed. There were no differences between the groups in the mating and fertility indices, and no differences with respect to pup number or viability or weight.

Task 4 was not performed on this study. After 7 days of vaginal smears to evaluate cyclicity, the control and high dose Task 2 mice were killed and necropsied. Female body weight at necropsy was reduced by 5%, while body-weight-adjusted organ weights were unchanged. Ante-mortem vaginal cyclicity was unaffected by caffeine exposure. Male body weight was unchanged by consumption of 0.05% caffeine, but adjusted liver weight was increased by 10%. Absolute testis weight dropped by 7% and adjusted seminal vesicles weight decreased by 12%. Sperm motility values for controls was low (47% motile), so the 21% reduction in the treated group should be viewed with caution. Similarly, the control epididymal sperm density was nearly equal to half of the subsequent control values for

this lab, so the significant increase in sperm density in the caffeine-treated group is likely erroneous.

The slight but significant reductions in (male) pup number, pup viability, and adjusted pup weight suggest that caffeine produced some slight reproductive toxicity. This occured in the presence of very slight indications of other toxicities (body or organ weight changes).

Test condition: Caffeine was tested simultaneously at two laboratories, each using a variation on the standard RACB study design. This study performed Tasks 1, 2, and 3, while the other study in mice performed Tasks 1, 2, and 4. Caffeine was among the very first compounds run at these labs using this protocol. Data on body weights, clinical signs, and food and water consumptions were collected during the dose-range-finding phase (Task 1), and used to set exposure concentrations for Task 2 at 0.0, 0.012, 0.025, and 0.05% in drinking water. Water was chosen to mimic the route of human exposure.

Test substance: caffeine; according to the authors, purity was > 98.5% (analyzed)

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
29-JAN-2003 (285)

Type: Fertility
Species: hen
Sex: male
Strain: no data
Route of administration: oral feed
Exposure Period: no data
Frequency of treatment: continuously in the diet
Doses: ca. 100 mg/kg (0.1% in the diet)
Control Group: no data specified

Method: other: no data
Year: 1976
GLP: no
Test substance: other TS

Result: Hens inseminated with sperm from treated roosters had reduced numbers of fertile eggs. In treated roosters, semen and sperm count were reduced 17-21 days after administration; and no semen could be collected after 30 days. According to the authors, the effects were reversible.

Test substance: caffeine
Reliability: (3) invalid
17-DEC-2001 (286)

Type: Two generation study
Species: rat
Sex: female
Strain: no data
Route of administration: oral unspecified
Exposure Period: 1 week prior to mating until day 20 post partum

Premating Exposure Period
female: 7 days
Doses: 4, 20, 126 mg/kg/d
Control Group: yes

Method: other: no data
Year: 1983
GLP: no data
Test substance: other TS

Remark: Females received the dose levels seven days before mating and through to 20 days of lactation; F1 offspring received the same treatment, mature F1 offspring were mated with untreated animals
Result: Females received the test substance starting seven days before mating and through to 20 days of lactation. F1 offspring were treated in the same manner. Mature F1 offspring were mated with untreated animals.
Pregnancy rate and reproduction were unaffected in F0 females and F1 males. Among F1 females, the pregnancy rate was unaffected but a decrease in the number of corpora lutea, implants and fetuses was observed in the high dose group. F2 fetuses of these high dose females were small and edematous.
Test substance: caffeine
Reliability: (4) not assignable
abstract
18-DEC-2001 (287)

Type: Two generation study
Species: rat
Sex: male
Strain: Wistar
Route of administration: gavage
Frequency of treatment: daily
Premating Exposure Period
male: 15 days
female: untreated
Doses: 30 mg/kg/d
Control Group: yes, concurrent vehicle

Method: other: no data
Year: 1988
GLP: no data
Test substance: other TS

Result: The effect of the test substance on male reproduction was studied over two generations. Male Wistar rats were administered an aqueous solution of the test substance or the vehicle only (F0 generation). According to the authors, the selected dose of 30 mg/kg/d was equivalent to human caffeine uptake of ca. 10-12 cups of brewed coffee daily. Beginning on day 15 of dosing, treated and control males were mated with untreated females. F1-pups were weaned at 23 days. At the age of ca. 100 days, F1 animals were randomly chosen for the breeding of the second generation (F2) which was obtained by back breeding. At the end of the breeding of the F1 generation, the F0 males were treated for another 38 consecutive days, Then, they were sacrificed; and their testes were examined microscopically.
In F1 offspring, significant fetal growth retardation (both sexes) and increased postnatal mortality of the pups between weeks 1 and 2 was noted. Many of these pups displayed characteristics of runts. Persistent caffeine effects were also seen in the F2 generation. From the female breeding line, pups of both sexes were born significantly heavier

when compared to their control counterparts. From the male breeding line, 33% of the litters conceived were aborted in utero, and among the F2 pups born runts were again evident.

Microscopical examination of the F0 males revealed marked degeneration characterized by significant overall size reduction, breakdown of the germinal epithelium, accumulation of cellular debris in the lumen of the seminiferous tubules, and significant reduction in the abundance of mature spermatozoa. On ultrastructural examination, there appeared to be genetic damage to the spermatozoa where nucleic cysts and pouches were seen.

Test substance: caffeine
Reliability: (3) invalid
not comparable with guideline studies
17-DEC-2001 (288)

Type: other: four generation study
Species: mouse
Sex: no data
Strain: no data
Route of administration: oral feed
Frequency of treatment: continuously
Doses: 4-5, 12-18, 25-39 mg/kg/d
Control Group: no data specified

Method: other: no data
Year: 1973
GLP: no
Test substance: other TS

Remark: Four generation study in mice continuously exposed
Result: In a four generation study, mice were continuously exposed to the test substance.
No consistent, dose-related effects on fertility, sexual maturation, mean litter size, weight of offspring at weaning, sex ratio or fetal abnormalities were observed. A few pairs exposed to the high dose level failed to produce litters; this was recorded only for the F1 brother-sister and the F3 matings.
Test substance: caffeine
Reliability: (2) valid with restrictions
18-DEC-2001 (289)

Type: other: multigeneration study
Species: rat
Sex: male/female
Strain: Wistar
Route of administration: drinking water
Frequency of treatment: continuously in the drinking water
Doses: 10 mg/kg/d
Control Group: no data specified

Method: other: no data
Year: 1981
GLP: no data
Test substance: other TS

Result: Exposure to the test substance was continued over five

successive sets of litters. Reduced growth and increased neonatal mortality were observed in the offspring over sequential pregnancies.

Test substance: caffeine

Reliability: (4) not assignable
secondary literature
18-DEC-2001 (290)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain: Osborne-Mendel
Route of administration: drinking water
Exposure period: days 0 to 20 of gestation
Frequency of treatment: continuously in the drinking water
Duration of test: until day 20 of gestation, postnatal day 0, or postnatal day 6
Doses: 24.7-29.0, 42.7-48.8, 70.6-75.1 mg/kg/d (180, 360, 700 ppm in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxity: = 180 ppm
NOAEL Teratogenicity: > 700 ppm

Method: other: no data
GLP: no data
Test substance: other TS

Remark: Number of females were mated are 60 (for control and lowest dose and 30 for mid and high dose group
Result: The rats were administered the test substance at concentrations of 0, 0.018, 0.036, and 0.07% (0, 180, 360, and 700 ppm) and were sacrificed at gestation day (gd) 20, postnatal day (pnd) 0, or pnd 6.
Maternal toxicity consisted of reduced drinking water and food consumption at 700 ppm (all groups) and retarded body weight gain at and above 360 ppm for rats sacrified on gd 20 and at 700 ppm for rats killed at pnd 0 and 6.
Results for animals killed on gd 20:
decreased number of viable fetuses, increased incidence of sternebral variations and specific other skeletal variations (mainly as signs of delayed ossification) at and above 360 ppm.
Results for animals killed on pnd 0:
no reproductive effects; at 700 ppm affected sternebral development and increased other skeletal variations as well as single cases of reduced ossification at 360 ppm and above.
Results for animals killed on pnd 6:
no reproductive effects; at 700 ppm transient impaired weight gain in neonates and reduced sternebral ossification.
General assessment:
Reversibility of most of the skeletal effects was shown
Test substance: caffeine, USP standard, purity 98.7%
Reliability: (2) valid with restrictions
13-AUG-2002 (291)

Species: rat **Sex:** female
Strain: Osborne-Mendel
Route of administration: drinking water
Exposure period: days 0 to 20 of gestation

Frequency of treatment: continuously in the drinking water
Duration of test: until day day 20 of gestation

Doses: ca. 10.1, 27.4, 50.7, 86.6, 115.8, 160.9, 204.5 mg/kg/d (70, 180, 360, 700, 1000, 1500, 2000 ppm in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxity: ca. 50.7 mg/kg bw
NOAEL Teratogenicity: > 204.5 mg/kg bw

Method: other: according to Collins, T.F.X. et al.: Regul. Toxic. Pharmac. 1, 355
Year: 1981
GLP: no data
Test substance: other TS

Result: The teratogenic potential of the test substance was investigated. Groups of 61 females were administered the test substance at concentrations of 0, 0.007, 0.018, 0.036, 0.07, 0.1, 0.15, and 0.2% in the drinking water, resulting in average daily uptakes of the test substance of 0, 10.1, 27.4, 50.7, 86.6, 115.8, 160.9, and 204.5 mg/kg, respectively. At day 20 of gestation, the dams were sacrificed, and the pups were excised by Caesarean section. No substance-related deaths occurred. Maternal food and water consumption was signifcantly decreased at doses of 0.1% and more. Maternal body weight gain was statistically significantly decreased at doses of 0.07% and more. Doses of 0.15% and 0.2% resulted in decreased implantation efficiency, increased resorptions, and decreased mean number of viable fetuses. The numbers of runts were significantly increased at dosages of 0.1% and more. At doses of 0.07% and more, fetal weights and lengths were decreased; and the number of edematous fetuses was increased. No dose-related gross anomalies were observed in any group. Sternebral ossification deficiencies were increased in all dosed groups except the lowest dose group. Skeletal ossifications deficiencies were increased in a dose-related manner at dose levels of 0.07% and above.
In summary, the no-observable effect (NOEL) for maternal toxicity was 0.036% (ca. 50.7 mg/kg/d); and the NOEL for developmental toxicity was 0.007% (ca. 10.1 mg/kg/d). No teratogenic effect was observed.
Test condition: Groups of 51 pregnant rats.
Test substance: caffeine; according to the authors, purity was >=98.5%
Reliability: (2) valid with restrictions
acceptable, well documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
08-AUG-2001 (292)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: drinking water
Exposure period: 5 weeks
Frequency of treatment: daily
Duration of test: 5 weeks
Doses: 30 mg/kg bw
Control Group: yes

Method: other
Year: 1978
GLP: no data
Test substance: other TS

Remark: In this older study with rats malformations were observed. In this combined subchronic, reproductive, developmental study with freshly percolated coffee in drinking water (9, 19, 39 mg/kg bw/d) or when caffeine was administered by gavage or in drinking water (30 mg/kg bw/d), cleft palates and delayed ossifications were observed (not dose -dependent). For coffee intake of 0%, 12.5%, 25% and 50% the number of observed fetuses with cleft palates were 1/423; 8/207; 5/225; 4/229, and for caffeine gavage intake 1/252, and caffeine in drinking water 2/245, only. Delayed ossification was found after coffee intake in 0/256; 8/128; 62/141; 11/148 and after caffeine intake in 12/171 and 15/160 animals respectively. The animals received coffee or caffeine
before mating, throughout gestation and up to 27 days after parturition. Effects on fertility, litter size and neonatal growth were not observed. No information about maternal toxicity was given in the report (Palm et al, 1978).

Test substance: Caffeine 30 mg/kg per gavage or drinking water.
Coffee as drinking fluid,(ca. 9, 19, 39 mg/kg Caffeine)

Reliability: (3) invalid
methodical deficiencies

12-AUG-2002 (293)

Species: monkey **Sex:** female
Strain: Macaca Fascicularis
Route of administration: drinking water
Exposure period: before, during and after pregnancy
Frequency of treatment: continuously in the drinking water
Duration of test: eight weeks before pregnancy to several months after pregnancy
Doses: ca. 10-15, 25-30 mg/kg/d (0.15, 0.35 mg/ml = 150, 350 ppm in the drinking water)
Control Group: yes, concurrent no treatment

Method: other: no data
Year: 1988
GLP: no data
Test substance: other TS

Result: Forty adult female monkeys were administered the test substance in the drinking water at concentrations of 0, 0.15 and 0.35 mg/ml before, during and after gestation. According to the authors, the concentrations administered corresponded to doses of ca. 0, 10-15, and 25-30 mg/k, respectively. Several parameters were evaluated.

Exposure to the test substance resulted in a dose-related increase in reproductive failure (stillbirths, miscarriages, decreased maternal weight gain). Analysis of blood and

24-hour urine samples (collected every 2 weeks) revealed a number of both pregnancy and treatment-related effects: decreased levels of serum cholesterol and triglyceride during pregnancy in all groups (pregnancy-related), increased levels of serum and urine creatinine in the treated groups (substance-related), unaltered serum glucose level in the high dose group (substance-related, this value usually declines during pregnancy), and depressed levels of serum estrogen in the high dose group (substance-related). According to the authors, this indicated that the test substance may influence maternal physiology during gestation in the monkey.

Additionally, the somatic development of the infants was monitored. Maternal blood and milk concentrations of the test substance were similar to infant blood concentrations. Infant body weights and somatic measurements were reduced over the first 30 days in males, as were a number of initial somatic measurements in male and female infants. The deficits were reversible and not evident after one year of age. Tooth eruption and milk consumption were not affected. According to the authors, this indicated that the test substance can alter infant somatic development when consumed during pregnancy.

Behavioural tests were conducted on the infants. At 30 days of age, the infants were trained to press a button for a formula reward, after which they performed on a variable ratio schedule for a 14-day period. Monitoring of feeding effect revealed that the treated infants spent significantly more time feeding than controls. On the variable ratio schedule, the high-dose group had consistently longer pause times and longer interresponses than controls. According to the authors, these results indicated that in utero exposure to caffeine and its metabolites resulted in altered behavioural patterns in infant monkeys.

Test substance: caffeine
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
18-DEC-2001 (294) (295) (296) (297) (298) (299)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: see remark
Frequency of treatment: daily
Duration of test: max. 12 months; see remark
Doses: 30, 60 mg/kg
Control Group: yes, concurrent vehicle

Method: other: no data
Year: 1992
GLP: no data
Test substance: other TS

Remark: After mating, F0 animals were treated daily by gavage from

day 2 to day 21 to obtain F1 animals. The F2 generation was obtained by breeding female F1 offspring with offspring from control and both dose groups. The second breeding was back-crossed to the F0 males avoiding father-daughter matings. Litters were removed 3 days after birth and the females were returned to the same familiar male for repeated breeding. The experiment was terminated before litter 8 in most cases and before any of the females were 12 months old.

Result: Exposure did not affect sexual receptivity, fertility, gestation length or maternal behaviour of the F1 females; however, parturition was prolonged.
The viability of the F2 generation was affected. Many F2 pups were born larger, and a significant proportion of litters (after the first two litters) were stillborn. The severity of the effects was dose-dependent and a NOEL was not established.

Test substance: caffeine

Reliability: (3) invalid
unsuitable test system

18-DEC-2001 (300) (301)

Species: rat **Sex:** female
Strain: Osborne-Mendel
Route of administration: gavage
Frequency of treatment: daily
Duration of test: day 0-19
Doses: 6, 12, 40, 80, 125 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: 12 mg/kg bw
NOAEL Teratogenicity: = 40 mg/kg bw

Method: other
Year: 1981
GLP: no data
Test substance: other TS

Remark: 61 rats were randomly assigned to each dose level, control rats were treated by gavage with distilled water at the same days (0-19).

Result: Six females died at the highest dose level. The experimental animals gained less weight during gestation than did the control (greates decease was seen during the first 7 days of dosing). Food consumption decreased primarily during the first week gestation. Two litters were totally resorbed at 80 mg/kg and four litters at 125 mg/kg. Resorptiuons increased at the dose levels 80 and 125 mg/kg. There were significant decreases in fetal weight and crown-crump lenght at 40 mg/kg. Ectrodactyly was seen only at the dose levels 80 and 125 mg/kg, along with assorted skeletal ossification problems such as misshappen centra, missing centra, reduced dorsal arch, reduced pubis, missing hind phalanges, reduced metacarpals, and reduced metatarsals. In addition, delayed ossification of the sternebrae was seen at all dose levels. No soft tissue variations appeared related to caffeine intake.

Test substance: caffeine, USP specification > 98.5%, 0.06% theobromine and

0.01% theophylline. Vehicle: destilled water, the solution for intubation was determined to be stable.
Reliability: (2) valid with restrictions
acceptable, publication meets basic scientific principles
16-AUG-2002 (302)

Species: rat **Sex:** male
Strain: Wistar
Route of administration: gavage
Exposure period: days 6 to 20 of gestation
Frequency of treatment: daily; as single bolus or as four divided doses every three hours
Duration of test: until day 21 of gestation
Doses: 10, 100 mg/kg/d
Control Group: no data specified

Method: other: no data
Year: 1987
GLP: no data
Test substance: other TS

Result: The rats were administered the test substance at dose levels of 10 or 100 mg/kg/d, either as single bolus or as four divided doses given at 3 hour intervals throughout the day. Controls were given distilled water at the same time. Maternal body weight and food and water consumption were reduced in the two groups receiving a total dose of 100 mg/kg/d and given 2.5 mg/kg four times daily. Dose-related decreases in fetal weight, placental weight and crown-rump length and related retardation of skeletal ossification were observed. Major fetal abnormities, mainly ectrodactyly were only seen in the group given 100 mg/kg in a single daily dose.
Test substance: caffeine
Reliability: (2) valid with restrictions
well documented
18-DEC-2001 (303)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: days 3 to 19 of gestation
Frequency of treatment: daily
Duration of test: until 9 weeks post partum
Doses: 5, 25, 50, 75 mg/kg/d
Control Group: no data specified

Method: other: no data
Year: 1986
GLP: no data
Test substance: other TS

Result: The aim of the study was to investigate the effect of the test substance on postnatal neurobehavioral development. Groups of 14-15 pregnant Sprague-Dawley (Charles River CD

strain) albino rats were administered the test substance in distilled water. Physical and behaviour observations were conducted on dams during gestation and lactation and on the offspring for up to 9 weeks of age. Observation included parturition parameters, body weights, food and water consumption, locomotor activity, open field activity, incisor eruption, auditory startle development, eye opening, vaginal opening, passive avoidance, shuttle box activity, pup retrieval, thermoregulation, testes decent, and air righting.
Decreased maternal weight and delayed postnatal development was noted in all treated groups. Some physical and neurobehavioural effects were observed in individual dams and offspring at all dose levels. Decreased fetal weights were seen at 50 mg/kg and above.
Incisor eruption was delayed in all groups, except the 25 mg/kg females. Auditory startle developed earlier at 5 mg/kg, but was delayed in 75 mg/kg males. Eye opening was delayed at both sexes at 25 mg/kg and above.

Test substance: caffeine

Reliability: (4) not assignable
secondary literature
18-DEC-2001 (304)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: gavage
Exposure period: days 6 to 16 of gestation
Frequency of treatment: daily
Doses: 56, 75, 100, 130, 180, 240, 320 mg/kg/d
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxity: = 56 mg/kg bw
NOAEL Teratogenicity: = 100 mg/kg bw

Method: other: no data
Year: 1968
GLP: no
Test substance: other TS

Remark: The lowest observed effect level for teratogenicity was 130 mg/kg. Teratogenic effects were only observed at dose levels that were maternally toxic and fetotoxic. According to the authors, administration of the test substance via diet produced no teratogenic effects.
Test substance: caffeine
Reliability: (4) not assignable
abstract
18-DEC-2001 (305)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: day 1 of gestation until sacrifice
Frequency of treatment: daily
Duration of test: until day 13, 14, 15, 16, or 20 of gestation
Doses: 30 mg/kg/d
Control Group: yes, concurrent vehicle

Method: other: no data
Year: 1990
GLP: no data
Test substance: other TS

Result: The aim of the study was to determine the influence of the test substance on the early differentiation of fetal rat ovaries and testes. Treatments were begun at day 1 of gestation and were continued until sacrifice on day 13, 14, 15, 16, or, for the ovaries only, day 20 of gestation. In the male fetuses, the test substance significantly inhibited differentiation of the interstitial tissue and Leydig cells; the number of Leydig cells exhibiting 3-beta-hydroxysteroid dehydrogenase activity was decreased and thus testosterone biosynthesis in the fetal testes was reduced (days 15 and 16). The test substance had also an effect on the early morphogenic organisation of the

seminiferous cord on day 13 where the aggregation of the Sertoli cells forming the seminiferous cord was slightly advanced in controls.
In the female fetuses, ovaries were similar to control in morphology, tissue arrangement and overall appearance.

The test substance did not affect the rate of early mitotic proliferation of germ cells, nor later in development, the numbers of cells entering meiosis.

Test substance: caffeine
Reliability: (3) invalid
unsuitable test system

18-DEC-2001 (306)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: days 7-19, 7-16, 16-19 or day 19 of gestation
Frequency of treatment: daily
Duration of test: until day 20 of gestaion
Doses: 100 mg/kg/d
Control Group: no data specified

Method: other: no data
Year: 1988
GLP: no data
Test substance: other TS

Result: Pregnant Sprague-Dawley rats were administered the test substance (in distilled water) at a dose of 100 mg/kg/d at different periods of gestation. Litters were removed on day 20 of gestation, weighed and examined for external and skeletal abnormalities. Decreased maternal and fetal body weight was observed in the group administered the test substance on gestation days (gd) 7-19. Marked effects on the fore- and hindpaw structures and greater incidence of bipartite and mishappen supraoccipital bones was seen in the groups treated on gd 7-19 and 16-19. The reduction in ossification was more pronounced in the group treated on gd 16-19. The rate of resorption or the litter size was unaffected in every group.

Test substance: caffeine
Reliability: (4) not assignable
secondary literature

18-DEC-2001 (307)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: gavage
Exposure period: days 7 to 17 of gestation
Doses: 150 mg/kg/d

Method: Chernoff-Kavlok teratogenicity screening test
Year: 1982
GLP: no data
Test substance: other TS

Result: The aim of this study was to validate the Chernoff-Kavlock assay. Groups of 9-15 pregnant Alpk:AP (Wistar-derived) rats were administered single doses of the test substance on days 7 to 17 of gestation. Offspring observations were litter

size and litter weight of live pups, and number of live and dead pups on days 1 and 5 post partum. No substance-related effects were observed. According to the authors, based on the results of this study, the test substance was predicted to have no fetotoxic or teratogenic effects.
Test substance: caffeine

Reliability: (4) not assignable
secondary literature
18-DEC-2001 (308)

Species: rat **Sex:** female
Strain: other: CD
Route of administration: gavage
Exposure period: days 1 to 19 of gestation
Frequency of treatment: daily
Duration of test: until day 20 of gestation
Doses: 40, 80 mg/kg/d
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: < 40 mg/kg bw
NOAEL Teratogenicity: > 80 mg/kg bw

Method: other: no data
GLP: yes
Test substance: other TS

Result: Groups of 20 pregnant rats were administered the test substance in distilled water and were sacrificed on days 20 of gestation. The fetuses were removed and examined for external, visceral or skeletal malformations.
Both dose levels significantly reduced maternal weight gain during gestation, but did not increase the prenatal death or malformation rate. Fetal weight was reduced in the high dose group.
Test condition: Groups of 20 pregnant rats.
Test substance: caffeine
Reliability: (2) valid with restrictions
guideline study (NTP)
Flag: Critical study for SIDS endpoint
06-NOV-2002 (309) (310)

Species: rat **Sex:** female
Strain: other: CD
Route of administration: gavage
Exposure period: days 1 to 20 of gestation
Frequency of treatment: daily
Doses: 10, 20, 40 mg/kg/d
Control Group: yes, concurrent vehicle

Method: other: National Toxicology Program (NTP)
GLP: yes
Test substance: other TS

Result: Groups of 12 pregnant rats were administered the test substance in distilled water and were allowed to litter. The

pups were subsequently evaluated for postnatal growth and several functional parameters (swimming, developmental activity, blood pressure and electrocardiographic recordings). There were no consistent effects of dose on any of the physical or functional parameters, although caffeine reduced maternal weight gain at all dose levels. According to the authors, these results suggested that administration of the test substance during gestation at doses of up to 40 mg/kg appered to have no adverse effect on offspring physical development, behaviour or cardiovascular function. NOAEL maternal <10 mg/kg bw/d, developmental toxicity 40 mg/kg bw/d

Test condition: Groups of 12 pregnant rats.
Test substance: caffeine
Reliability: (2) valid with restrictions
guideline study (NTP)
Flag: Critical study for SIDS endpoint
06-NOV-2002 (309)

Species: mouse **Sex:** female
Strain: CD-1
Route of administration: gavage
Exposure period: days 8 to 12 of gestation
Frequency of treatment: daily
Duration of test: until day 3 post partum
Doses: 200 mg/kg/d
Control Group: yes

Method: Chernoff-Kavlok teratogenicity screening test
Year: 1982
GLP: no data
Test substance: other TS

Remark: A battery of 28 compounds of known teratogenic potential including the test substance was assayed for an evaluation of the teratogenicity screen.
General procedure:
Groups of 24 to 30 pregnant mice were administered the test substance on gestation days 8 to 12 at doses of the medium tolerated dose (MTD). Litters were counted and weighed at days 1 and 3 post partum. Maternal body weights were recorded.
Result: Maternal body weight gain was significantly lower than control during treatment. Average litter weight was significantly lower than control when evaluated at day 3 post partum.
Test substance: caffeine
Reliability: (3) invalid
screening test
18-DEC-2001 (311) (71)

Species: mouse **Sex:** female
Strain: CD-1
Route of administration: gavage
Exposure period: days 6 to 15 of gestation
Frequency of treatment: daily

Doses: 50, 100, 250, 400 mg/kg/d
Control Group: no data specified
NOAEL Maternal Toxity: = 50 mg/kg bw
NOAEL Teratogenicity: = 100 mg/kg bw

Method: other: no data
Year: 1991
GLP: no data
Test substance: other TS

Result: Reduced maternal body weight gain was observed at doses of 100 mg/kg/d and more. Developmental effects (on fetal weight and ossification) were observed at doses of 250 mg/kg/d and more.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
18-DEC-2001 (312)

Species: mouse **Sex:** female
Strain: CD-1
Route of administration: gavage
Exposure period: day 8 of gestation
Frequency of treatment: single dose
Duration of test: until day 18 of gestation
Doses: 350 mg/kg
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: other TS

Result: The aim of the study was to determine the effect of acute maternal toxicity on fetal development. The dams were administered a slightly to moderately toxic dose of the test substance in distilled water on day 8 of gestation and were sacrificed on day 18 for evaluation of developmental toxicity. No difference between treated and control group was seen concerning embryonic resorption, growth, skeletal development, or terata. Supernumerary ribs was the only observed fetal effect with a linear inverse relationship between maternal body weight gain during gestation.
Test substance: caffeine
Reliability: (4) not assignable
screening
18-DEC-2001 (313)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: days 10 to 22 of gestation
Frequency of treatment: continuously in the diet
Duration of test: until day 22 of gestation
Doses: 5, 10, 20 mg/kg
Control Group: yes, concurrent no treatment

Method: other: no data
GLP: no data
Test substance: other TS

Result: The effect of the test substance on fetal rat brain parameters was studied in 4 groups of 4 pregnant rats. From gestational day 10 onwards, the dams were fed a diet containing 20% of protein and the test substance at concentrations providing dose levels of 0 (control), 5, 10, and 20 mg/kg body weight (concentration was adjusted to body weight). On day 22 of gestation, pups were delivered surgically; their brains were rapidly removed and analysed for DNA protein, cholesterol, zinc and alkaline phosphatase activity as well as for plasma and brain caffeine levels (treated groups only). The dams' brains were analysed for the same parameters.

In the pups, brain weights, DNA content, cholesterol and zinc concentration, and alkaline phosphatese activity of the brains were decreased showing a trend to dose-response. Protein concentration of the brain was increased in the high dose pups. The biochemical parameters of the dams were similar in all groups, except an increased cholesterol concentration in the treated groups. Plasma and brain levels of the test substance were higher in the high dose group than in the mid and low dose groups.
According to the authors, these results indicated that maternal caffeine intake exerted different effects on fetal brain growth, while the effects on the dams' brain was relatively minor.

Test substance: caffeine
Reliability: (3) invalid
unsuitable test system, only brain observation after caffeine intake

18-DEC-2001 (314)

Species: mouse **Sex:** female
Strain: ICL-ICR
Route of administration: i.p.
Exposure period: day 12 of gestation
Frequency of treatment: single dose
Doses: 200, 250 mg/kg
Control Group: yes, concurrent vehicle

Method: other: no data
Year: 1969
GLP: no data
Test substance: other TS

Remark: NOEL for maternal toxicity can not be given since data were insufficient reported; study does not meet current standard
Result: About 30% of the high dose females died. Dyspnoea and convulsions were observed at 200 and 250 mg/kg. Increased resorptions were recorded for the high dose group. Fetal body weight was decreased in both dose groups. Malformations occurred dose-dependently in all fetuses, these included cleft palate, digital defects and macrognathia; subcutaneous hematomas were also observed.
Test substance: caffeine
Reliability: (4) not assignable
documentation insufficient for assessment

18-DEC-2001 (315)

Species: mouse **Sex:** female
Strain: other
Route of administration: i.p.
Exposure period: one of days 7 to 14 of gestation
Frequency of treatment: single dose
Doses: 250 mg/kg
Control Group: no data specified

Method: other: no data
GLP: no

Test substance: other TS

Result: Increases of fetal resorptions, cleft palate and digital defects dependent on the day of treatment were noted.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
18-DEC-2001 (316)

Species: mouse **Sex:** female
Strain: other: TO
Route of administration: i.p.
Exposure period: days 10 to 14 of gestation
Frequency of treatment: daily
Duration of test: until day 18 of gestation
Doses: 200 mg/kg/d
Control Group: yes

Method: other: no data
Year: 1998
GLP: no data
Test substance: other TS

Result: The malformation of the joints and bones induced by the test substance was studied in two groups of TO mice. One group was administered the test substance on days 10 to 14 of gestation; fetuses were collected on day 18 of gestation. The second group was prepared as a control. A modest increase in resorption, and significant reduction of both body weight and length of the fetuses was noted. Limb malformations were found in 40%. Alizarin and Alcain blue revealed reduction in endochondral ossification, especially in small bones. Histologically, the large joints (knee and hip joint) were not affected while small joints showed some defects (absence of the joint cavity). Absence of the forearm and/or the hand was seen in some fetuses. These anomalies were common in th 11th day of gestation group. According to the authors, these results suggested that a high dose of the test substance retarded the skeletal growth and inhibited the differentiation of some of the small joints.
Test substance: caffeine
Reliability: (4) not assignable
abstract

18-DEC-2001 (317)

Species: mouse **Sex:** female
Strain: other: CF-1
Route of administration: i.p.
Exposure period: days 11 and 12 of gestation
Frequency of treatment: daily
Duration of test: until day 17 of gestation
Doses: 25, 100, 200, 250 mg/kg/d (129, 515, 1030, 129 umoles/kg)

Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 25 mg/kg bw
NOAEL Teratogenicity: = 200 mg/kg bw

Method: other: no data
Year: 1987
GLP: no data
Test substance: other TS

Result: The mice were administered the test substance in 0.5% methylcellulose on days 11 and 12 of gestation and were sacrificed on day 17 of gestation. The implants were removed and classified.
No effect was seen at a dose level of 25 mg/kg. Doses of 100 mg/kg were maternally toxic and embryotoxic; decreased maternal body weights were recorded. At 200 mg/kg and more, increased resorption rates, decresed fetal body weights and malformations (cleft palate, ectrodactyly, and micrograntia) was observed.
Test substance: caffeine
Reliability: (3) invalid methodological deficiencies
18-DEC-2001 (318)

Species: rat **Sex:** female
Strain: other: CD
Route of administration: i.v.
Exposure period: day 11 of gestation
Frequency of treatment: single dose
Duration of test: until postnatal day 240
Doses: 75, 150 mg/kg
Control Group: yes, concurrent vehicle

Method: other: National Toxicology Program (NTP)
Year: 1987
GLP: yes
Test substance: other TS

Result: Groups of 15 pregnant rats were administered a single i.v. injection on day 11 of gestation and allowed to litter. Pups were evaluated for physical defects and functional abnormalities. Groups of pups were sacrificed on postnatal days (PND) 225, 90, 120, or 240 and their skeletons were examined for defects.
At birth, 15% of the high dose pups had tail defects; at later ages, 50% of the pups of this group showed defects in the lumbar and caudal region. However, viability and growth rate was unaffected, and gait and landing foot spread patterns were normal. Alterations in other functional endpoits were evident. Such changes included higher levels of immobilization during swimming (150 mg/kg), elevated activity levels (75-mg/kg-males on PND 12, 16, and 20), and increased systolic blood pressure (both groups at 4 months of age).
According to the authors, these results suggested that physical and functional abnormalities were produced by i.v.

administration of the test substance given during organogenesis, but that the functional changes were not necessarily related to the physical abnormalities.
Test condition: Groups of 15 pregnant rats.
Test substance: caffeine
Reliability: (2) valid with restrictions
no guideline study, only one unphysiological application.
07-NOV-2002 (319)

Species: mouse **Sex:** female
Strain: no data
Route of administration: oral unspecified
Exposure period: during organogenesis
Duration of test: until day 22 post partum
Doses: 200 mg/kg/d
Control Group: no data specified

Method: Chernoff-Kavlok teratogenicity screening test
Year: 1984
GLP: no data
Test substance: other TS

Result: No difference in viability was seen at day 3 post partum between treated and control groups. Lower body weights of the pups were noted at days 3 and 22 post partum. There was no effect on the reproductive development and morphology of the offsprings.
Test substance: caffeine
Reliability: (3) invalid
screening test
18-DEC-2001 (320)

Species: mouse **Sex:** female
Strain: NMRI
Route of administration: oral unspecified
Exposure period: day 2 of gestation
Frequency of treatment: single dose
Duration of test: until day 17 of gestation
Doses: 100 mg/kg
Control Group: yes

Method: other: no data
Year: 1987
GLP: no data
Test substance: other TS

Result: The potentiating effect of the test substance on embryotoxicity of cyclophosphamide (CPA) was studied. Pregnant mice were administered the test substance on day 2 of gestation. Uteri were excised on day 17 and examined for dead and resorbed embryos; the surviving embryos were examined for external, internal and skeletal malformation. No increase in embryolethality was seen.

Other groups were administered the test substance in

combination with CPA (20 mg/kg), a known embryotoxic compound. The embryotoxicity of CPA did not increase when the test substance was either given 6 h before of simultaneously with CPA on day 2. However, when the test substance was given 6 h after CPA administration, a potentiated increase of embryolethality was observed.
Test substance: caffeine

Reliability: (3) invalid
combination study with cyclophosphamide, only one dose tested
18-DEC-2001 (321)

Species: rat **Sex:** female
Route of administration: other: drinking water, gavage
Doses: 14, 40, 125 mg/kg

Method: other: no data
Year: 1986
GLP: no data
Test substance: other TS

Result: Pregnant rats were administered the test substance either in the drinking water or by gavage at doses of 14, 40, and 125 mg/kg. Teratogenic effects were observed in rats administered 125 mg/kg by gavage.
Test substance: caffeine
Reliability: (4) not assignable
secondary study
18-DEC-2001 (322)

Species: rabbit **Sex:** female
Route of administration: other: drinking water, gavage
Doses: 14, 40, 125 mg/kg

Method: other: no data
GLP: no data
Test substance: other TS

Result: Pregnant rabbits were administered the test substance either in the drinking water or by gavage at doses of 14, 40, and 125 mg/kg. No teratogenic effects were observed.
Test substance: caffeine
Reliability: (4) not assignable
secondary study
18-DEC-2001 (322)

Species: mouse **Sex:** male/female
Strain: no data
Route of administration: s.c.
Exposure period: see freetext
Frequency of treatment: daily
Duration of test: see freetext
Doses: 18 mg/kg/d
Control Group: yes

Method: other: no data
Year: 1993
GLP: no data
Test substance: other TS

Result: The reproductive and teratogenic effect of the test substance was studied in 5 groups of inbred mice. The test substance was administered daily by subcutaneous injection at a dose level of 18 mg/kg. In detail, the five groups were treated as follows:
- males; dosed for 21 days, then mated with control females
- pregnant females; dosed from gestations day (gd) 1 and throughout embryonic development
- females; dosed 21 days prior to mating and throughout embryonic development, mated with control males
- males and females; dosed 21 days prior to mating, mated with each other, treatment of females continued throughout embryonic development
- untreated controls (males and females)

In parent animals, the test substance increased death rate and percentage of abortion and decreased maternal body weight gain and uterine weight. Lethargy and a decrease in mating rate was noted for treated females. In treated males, increased activity and normal mating rate was noted. Marked histopathological alterations of ovaries and testes was observed.
In the treated groups, the incidence of resorptions (early fetal death) and stillbirth (late fetal death) was increased. Retarded ossification and shortness of some bones was observed. Skull, sternum, girdles and limbs were the main bones affected.
Test substance: caffeine
Reliability: (3) invalid
unsuitable test system
18-DEC-2001 (323) (324)

Species: rabbit **Sex:** female
Strain: no data
Route of administration: unspecified
Exposure period: days 1 to 25 of gestation
Doses: 100 mg/kg
Control Group: no

Method: other: no data
GLP: no
Test substance: other TS

Result: Induction of ectrodactyly in 6/64 offsprings.
No further information available.
Test substance: caffeine
Reliability: (4) not assignable
secondary literature
18-DEC-2001 (325)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Remark: remark on selection of studies
The scientific literature of caffeine comprises thousands of published studies and reviews due its containment in beverages (coffee, tea, cocoa, cola drinks, etc.) and is use as pharmaceutical. With a focus on health and safety issues comprehensive reviews including those of the International Agency for Research on Cancer (IARC), Nehlig and Debry, 1996 and Emerson and Chappel, 1999 studies cited in these reviews were choosen for the data set of caffeine. For selected endpoints (e.g. reproductive toxicity) additonal up-date retrieval were done.

27-AUG-2001

Remark: review (general)
Review on research topics: caffeine consumption, caffeine intake levels in children, caffeine intake and bone density,
undestanding balance studies as they relate to caffeine and calcium metabolism, effect of caffeine, alcohol and tobacco on bone density, medium-term carcinogenicity bioassay, health professionals follow-up study, Framingham study, Norwegian study, meta-analysis of coffee and coronary heart disease, boiled/filtered coffee and cholesterol, central pathways affected by xanthines, behavioural aspects of caffeine, caffeine, brain calcium and behaviour, chronic effects of caffeine on function of adenosinergic, dopaminergic and cholinergic systems, methodological issues in assessing caffeine consumption/exposure, caffeine cinsumption and malignancy in women, systematic evaluation of environmental reproductive risk: caffeine as a model, maternal caffeine consumption and foetal behaviour in normal third-trimester pregnancy, endurance performance and caffeine ingestion, mehtylxanthine metabolism and epinephrine during exercise, metabolic adaptations to caffeine ingestion, caffeine and short intense exercise, caffeine use and drug abuse, discriminability of caffeine in humans, regular caffeine use does not imply dependence, caffeine compared with traditional drugs of abuse, historical research into mental effects of caffeine, caffeine and stress: psychological interactions, electrophysiological brain activity and attention, effects of caffeine on the performance and mood of subjects with low levels of arousal.

14-FEB-2001 (326)

Remark: review (general)
Review on research topics: caffeine metabolites, effects of prenatal caffeine exposure on growth and development of children, effects of caffeine on cognitive function,

caffeine and cardiac arrhythmias, coffee and cholesterol, and caffeine and baroflex control.

14-FEB-2001 (327)

Remark: In sum, the epidemiologic data on the role of caffeine in most of the major chronic diseases studied - including myocardial infarction, cancer of selected sites, and unfavourable pregnancy outcome - is reassuring in that no marked elevations in risk habe been found in the majority of studies for most diseases and, even for those conditions for which a small number of studies showed elevated risks, dose-response relations with caffeine were usually not demonstrated. It should acknowledged that some studies have studied coffe only, some coffee and tea only, while others have created indices of caffeine or methylxanthine exposure that included cola drinks and chocolate; all studies have depended on patient report of consumption, often requiring recall of past exposures. Many studies are not comparable because very different patient populations were studied, confounding variables were often not taken into account, caffeine exposure categories were defined using very different cut-points, numbers of patients differed dramatically, and others.
review (general)

14-FEB-2001 (328)

Remark: review (general)
review on health effects of coffee, tea, and their major methylxanthine components

27-AUG-2001 (329)

Remark: Absorption from gastrointestinal tract is rapid, virtually complete and dependent on the pH. Plasma curves suggest that there is no pronounced first-pass effect. After oral ingestion, peak plasma levels range from 15 to 120 minutes and are dependent on gastric emptying and the presence of dietary constituents.
Distribution is rapid and uniformly into body fluids. The volume of distribution range from 0.5 to 0.8 l/kg. 10-35% is bound to plasma proteins (mainly albumin) over a wide range of concentrations. The binding capacity to breast proteins is about 3.2%.
Elimination is by first-order kinetics described by one-compartment open model system. The half-life decreases after birth and reaches adult values (2.5-4.5 h) at ca. 6 months of age. Serum clearance is 31.5 ml/kg (1-2.5 months old child) and ca. 330 ml/kg (5-6 months old child); values of ca. 155 ml/kg are recorded for adults (smokers and non-smokers).
The metabolic disposition or volume of distribution do not differ between man and woman. However, the use of contracepives double the half-life, and the half life is also prolonged during pregnancy while clearance is increased
by more than 3-fold 2-12 weeks post partum. Concentrations

in human and fetal gonads are similar to plasma.
A small percentage is excreted unchanged in the urine.
Excretion is also found in bile, saliva, semen and breast milk.

The metabolism is the rate-limiting factor for plasma clearance. Caffeine is metabolized by hepatic microsomal enzymes, while no significant metabolism occurs in other organs. After oral ingestion, plasma concentrations of theophylline and theobromine show a small increase, while a 10-fold higher paraxanthine is observed. The amount of urinary metabolites depends on the rate of each transformation step, the distribution of metabolites, their plasma concentration and their renal excretion.
The most important metabolic pathway is demethylation (95%); only 5% gives trimethyl derivatives. Paraxanthine is formed and is the precursor of 5-acetylamino-6-formylamino-3-methyluracil (which is only found in humans). The variability of the production and excretion rates of acetylated urinary metabolites is related to acetylation polymorphism. Fecal excretion of 2.5% also occurs with the important products being 1,7-dimethyluric acid, 1-methyluric acid, 1,3-dimethyluric acid, 1,3,7-trimethyluric acid and unchanged caffeine.
kinetics (absorption, distribution, metabolism and excretion, review)

28-MAR-2001 (330) (331) (332)

Remark: kinetics (absorption, distribution, metabolism and excretion, review)
review on absorption, distribution, metabolism, and elimination of caffeine

14-FEB-2001 (333)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The emptying and absorption of caffeine (175 mg caffeine in 350 ml) from the stomach were studied in six healthy subjects compared to water of equal volume. Emptying of caffeine and water proceeded at the same rate up to 20 min at which 86 % had left the stomach. Absorption of caffeine was directly related to the time present in the stomach and at 20 min. reached a peak of 16.3 +- 1.1% of the ingested dose. In a further study with six subjects ingested dose buffered to pH 1.0, 2.1, 3.5, 7.0 and 9.0 and gastric emptying delayed by glucose. Absorption of caffeine at pH 1.0 was negligible and increased siginificantly with increased pH up to a peak of 21.5 % of the ingested dose at pH 7.0.

13-MAR-2001 (334)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The rise in plasma-caffeine concentration following ingestion of 150-160 mg caffeine given in the form of tea, coffee and Coca Cola was investigated in three male volunteers. Maximum plasma-caffeine concentrations of about 7 mg/dl were reached at 30 min. after coffe and tea but at 60-120 min after Coca-Cola.

13-FEB-2001 (335)

Remark: Caffeine disposition was studied in four men after 1, 5 and 10 mg/kg per oral. Plasma peak was reached 47 +- 5 min. after dosing (mean concentration of 8.3 +- 0.1 µg/ml), absorption rate constant was 6.3 +- 1.9 and elimination rate constant 0.11 +- 0.02 hour-1. 99 % of the administered dose was absorbed. The least polar metabolites 3,7-diemthylxanthine, 1,3-dimethylxanthine, and 1,7-dimethylxanthine could be measured in plasma. About 85% of the dose was recovered in thr urine within 48 hours. The main excreted metabolites were 1-methyluric acid, 1-methylxanthine, 1,7-dimethyluric acid, 7-methylxanthine, and 1,7-dimethlyxanthine.
kinetics (absorption, distribution, metabolism and excretion)

14-MAR-2001 (336)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The absolute bioavailibility of orally administered caffeine was investigated in 10 healthy adult male volunteers. The subjects were administered a 5 mg/kg dose of caffeine (oral or i.v.). The oral absorption was very rapid, reaching a peak plasma concentration after 29.8 +- 8.1 min. The rapid absorption resulted in essentially complete bioavailability of the oral caffeine, F(%)=108.3 +- 3.6%. The caffeine plasma half-lives varied from 2.7 to 9.9 hours.

13-FEB-2001 (337)

Remark: In vivo and in vitro studies have shown that caffeine is bound (10-30%) to plasma albumin over a wide range of concentrations (1-100 µg/ml), ages, and species examined. kinetics (absorption, distribution, metabolism and excretion, review)

14-MAR-2001 (338)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Plasma kinetics of caffeine and dimethylxanthines was studied in humans. Before caffeine administration, low but significant amounts of caffeine and dimethylxanthines were found in the plasma of all the 6 subjects tested. After caffeine administration (8 mg/kg bw), a small increase was observed for theobromine and theophylline.

14-MAR-2001 (339)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Nine healthy subjects received, in randomized five day treatment blocks, placebo, 4.2 mg/kg/d caffeine (low dose) or 12 mg/kg/d caffeine (high dose) in six divided doses spaced throughout the day. On the 3rd day, 25 mg labelled caffeine was administered i.v.. Clearance fell from 0.118 (placebo) to 0.069 (low dose) to 0.054 l/h/kg (high dose). The formation and metabolic clearance of paraxanthine (major primary metabolite) decreased comparing the low and high dose, indicating a probably saturable process. The authors concluded a dose-dependency of the metabolism of caffeine and its metabolites, leading to disproportionate increases in blood levels with increasing daily doses of caffeine.

13-FEB-2001 (340)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Single oral doses of 70, 200, and 300 mg/kg to healthy subjects exhibited dose-dependent pharmcokinetics indicating a saturable caffeine metabolism in the tested dose range.
At the low, mid and high dose level, mean half time (t1/2) was 4.5, 6.0, and 6.4 h, respectively; clearance was 1.52, 1.14, and 1.08 ml/min/kg, respectively.

13-FEB-2001 (341)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The developmental changes in caffeine elimination were studied in 7 infants aged between 2.5 weeks and 6 months. Adult plasma clearance rate of caffeine was achieved at 3 to 4.5 months of age. Plasma half-life elimination rate reached adult levels after 3 to 4.5 months and seemed to exceed adult capacity thereafter.

13-FEB-2001 (342)

Remark: Elimination of caffeine in 15 healthy term newborn infants, who have acquired substantial amounts of caffeine transplacentally. Caffeine was found in every cord plasma sample. Its mean concentration was 1.4 mg/l. The plasma elimination half-life time for caffeine varied from 31 to 132 hours, with a mean of 82 hours.
kinetics (absorption, distribution, metabolism and excretion)

14-MAR-2001 (343)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Kinetics parameter of caffeine were measured in 9 pregnant women and 4 women 4 days post partum. The result showed a significant prolongation of caffeine elimination in pregnant women. Normal kinetics parameters seem to be restored as soon as 4 days post partum.

13-FEB-2001 (344)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The effect of oral contraceptive steroids (OCS) on the disposition and elimination of caffeine was examined in 13 healthy males, nine healthy females taking no OCS, and nine healthy females on OCS. The elimination half-time was significantly prolonged in women on OCS (10.7 vs. 6.2 hours) as compared to women taking no OCS. Women on OCS had a significantly lower total plasma clearance (0.79 vs. 1.3 mml/min/kg) and free clearance (1.12 vs. 1.97 ml/min/kg) than women not taking OCS. When women taking no OCS were compared with men, all kinetic parameters were similar except for volume of distribution, which was significantly larger in the women.

13-FEB-2001 (345)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The effect of chronic (> 3 months) administration of low-dose oestrogen-containing (< 50 µg oestrogen) oral contraceptives (OCS) on the kinetics of caffeine has been examined in 9 treated females mated with 9 controls. Each subject received 162 mg caffeine base orally. OCS sunjects had a prolonged elimination half-life of caffeine (7.88 vs. 5.37 h). Plasma clearance decreased (1.05 vs. 1.75 ml/min/kg) and apparent volume of distribution did not change. Peak plasma concentrations were 3.99 vs. 4.09 µg/ml and time to peak concentration 1.52 vs. 0.79 hours.

13-FEB-2001 (346)

Remark: kinetics (absorption, distribution, metabolism and excretion)

The elimination of caffeine from salvia was compared in groups of healthy smokers (n=13) and nonsmokers (n=13). Mean caffeine t 1/2 in smokers (3.5 hr) was shorter than that in the nonsmokers (6.0 hr). The body clearance of caffeine in the smokers (155 ml/kg/hr) was greater than that in the nonsmokers (94 ml/kg/hr). No significant difference was noted in the apparent volume of distribution in smokers (720 ml/kG) and nonsmokers (619 ml/kg).

13-FEB-2001 (347)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The effect of smoking on caffeine elimination was measured in 7 healthy volunteers and in 18 smoking and in 30 nonsmoking patients with alcoholic liver cirrhosis following oral application of 366 mg caffeine. In an intraindividual experiment in smoking healthy probands, caffeine clearance decreased from 118 to 77 ml per min after abstaining cigarette smoking for 3 weeks. In a control group without liver disease, caffeine clearance of 114 per min in smokers and 64 in nonsmokers. Smoking and nonsmoking patients with alcoholic liver cirrhosis did not differ with respect to clinical and laboratory data and hexobarbitone elimination.
However, caffeine clearance was 63 per min in smoking patients compared to 34 ml per min in nonsmokers. Fasting plasma concentrations of caffeine were higher in nonsmokers (5.1 µg/ml) than in smokers (2.1 µg/ml).

13-FEB-2001 (348)

Remark: Caffeine equilibrates freely between plasma and tissue water in the case of human ovary and testis, and also between maternal plasma and human 7-8 week fetus. Tissue sample were obtained from surgical specimens or abortions. Caffeine (574 mg) was given by intravenous infusion over a period of 5 min.
kinetics (absorption, distribution, metabolism and excretion)

13-FEB-2001 (349)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Simultaneous serum and cerebrospinal fluid samples were obtained from seven premature infants who were receiving methylxanthines for control of apnea. CSF concentration of caffeine was slightly lower than that of serum. The realtionship of caffeine in serum and ventricular fluid was close to unity.

13-FEB-2001 (350)

Remark: Excretion of caffeine in semen was studied in 10 healthy volunteers receiving 200 or 400 mg caffeine per oral. In the semen of six subjects, in each of whom 2 samples were

recovered during the elimination phase, the elimiantion half-life time of the drug ranged from 2.7 to 4.4 hours.

The concentration ratio of caffeine between blood and semen is about 1.
kinetics (absorption, distribution, metabolism and excretion)
14-MAR-2001 (351)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Kinetics of caffeine was investigated in microsomes isolated from livers of human kidney donors. PAH-inducible isozyme of cytochrome P-450 is involved in metabolism of each of the four detectable primary metabolites of caffeine:
1,7-dimethylxanthine, 3,7-diemthylxanthine,
1,3-dimethylaxanthine, and 1,3,7-trimethyluric acid.
27-FEB-2001 (352)

Remark: Accumulation of serum caffeine was observed in a patient with severe liver disease. Serial serum caffeine concentrations revealed a serum elimination half-life time of 96 hours.
kinetics (absorption, distribution, metabolism and excretion)
13-FEB-2001 (353)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Nine healthy volunteers participated in a randomised cross-over study and received caffeine in doses ranging from 1.52 mg/kg to 17.53 mg/kg. The maximum caffeine concentration in urine recorded was 14 µg/ml, 3 hours after ingestion. The mean recovery of caffeine in urine was between 0.74% and 0.91% of the administered dose.
14-MAR-2001 (354)

Remark: kinetics (absorption, distribution, metabolism and excretion, review)
review on metabolism of coffee constituents: minerals, carbohydrates, proteins and amino acids, lipids, aliphatic compounds, aromatic compounds, heterocyclic compounds, and alkaloids (incl. caffeine). Five uracil derivates have now been identified, produced from caffeine, theobromine, and paraxanthine. Except the formation of 1-methyluricc acid from 1-methylxanthine where xanthine oxidase is involved. All of the other metabolic tranformations were observed with liver microsomal enzymes.
14-MAR-2001 (355)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Radiolabelled caffeine was administered orally at 5 mg/kg to adult, male volunteers. The elimination half-life time of caffeine in both serum and salvia was appr. 3 hours,

with the concentration of caffeine in salvia samples ranging from 65 to 85% of that found in the serum samples.

The major metabolites found in serum and salvia were the dimethylxanthines. The major urinary metabolite 5-acetylamino-6-amino-3-methyluracil ranged from 7 to 30 % of the administered dose. The other principal urinary metabolites were 1-methylxanthine at appr. 18% of the administered dose and 1-methyluric acid at 15%.

27-FEB-2001 (356)

Remark: Dimethylxanthine formation from caffeine in plasma and salvia was investigated in ten healthy volunteers after oral ingestion of 200 mg caffeine. Salvia concentration of caffeine, paraxanthinee, and theophylline were lower than plasma concentrations, whereas theobromine concentrations in plasma and salvia were similar. The AUC for diemthylxanthine in plasma underestimates the formation of paraxanthine, overestimates the formation of theobromine and gives a similar formation of theophylline from caffeine, as judged from the urinary metabolites formed through the paraxanthine, theobromine and theophylline pathway.
kinetics (absorption, distribution, metabolism and excretion)

27-FEB-2001 (357)

Remark: Low doses (up to 2 ug/ml in the blood) stimulate the central nervous system while high blood concentrations (10-30 ug/ml) produce restlessness, excitement, tremor, tinnitus, headache, and insomnia. Caffeine can induce alterations in mood and sleep patterns, increase urine production and gastric acid secretions, alter myocardial functions and increase plasma catecholamine levels and plasma renin activity. Excessive consumption may lead to an anxiety neurosis called caffeinism.
Acute toxicity is not very common, although some adverse effects (e.g. gastric symptoms, insomnia, diuresis) are the results of an overdose.
toxic effects (review)

07-MAR-2001 (331)

Remark: review on toxicity to humans: Severe intoxication due to caffeine is not common. Symptoms of caffeine toxicity in adults were: acute psychosis, anorexia, anxiety, cardiac arrhythmia, convulsions, coma, confusion, depression, diarhoea, disorientation, flushing, headache, haematemesis, hypokalaemia, insomnia, metabolic acidosis, muscular twitching, nervousness, seizures, tremor, and vomiting. Caffeine may cause severe intoxications and even death. Habitual users of methylxanthines (especially caffeine) develop a tolerance.
toxic effects (review)

07-MAR-2001 (358)

Remark: Pharmacological/toxic effects of caffeine were summarized. An intake of one cup of coffee (100-150 mg caffeine) can increase alertness, reduce fatigue, and stimulate gastric

acid secretion. The amount of 3 or more cups of coffee may cause mild anxiety, headache, diuresis, rapid breathing, insomnia, tachycardia, and tremors.

Doses of more than 5000 mg can cause convulsions, coma, and death. Reactions to caffeine vary widely from person to person.
toxic effects (review)

14-FEB-2001 (359)

Remark: review on kinetics, effects on central nervous system, cardiovascular system, renal function, respiratory system, and gastrointestinal effects of caffeine.
toxic effects (review kinetics, pharmacology)
27-FEB-2001 (360)

Remark: The lowest fatal doses in humans were 3.2 g administered intravenously to a 35-year-old woman, and 5.3 g self-administered orally in a 5-year-old girl, of which 2.3 g was found in the stomach. It is concluded that the lowest oral dose that might be fatal to an adult is probably in the
order of 5 g, a dose that is unlikely to be encountered through beverage consumption.
toxic effects (fatal dose)
15-FEB-2001 (361)

Remark: It has been estimated that 5 to 10 gm. may be fatal in man.
toxic effects (fatal dose)
26-FEB-2001 (362)

Remark: Doses larger than 300 mg caffeine are anxiogenic, producing symptoms indistinguishable from anxiety neurosis including insomnia, headache, irritability, tremor, nausea, and diarrhoea. Sensitivity to these effects varies among individuals, depending on tolerance, rate of absorption, and metabolism.
toxic effects (poisoning)
15-FEB-2001 (363)

Remark: The widespread of use of caffeine is most commonly linked to the stimulatory action it has on the central nervous system.
Generally, adverse effects include gastrorrhea, insomnia, and diuresis. Tolerance and withdrawal symptoms have been observed and excessive consumption can lead to an anxiety neurosis condition (caffeinism). The actions of caffeine may involve its effects on neurotransmitter turnover and metabolism; its promotion of the cellular messenger, cAMP, its sensitization of the calcium releasing mechansims of cellular recticulum; or its antagonism of the autoacoid, adenosine. Caffeine lethality is rare in man but caffeine poisoning with its gastrointestinal, CNS, and cardiovascular stimulation could especially be hazardous to children. Nothing but circumstantial evidence implicates caffeine as a human carcinogen or teratogen.

toxic effects (poisoning, review)
14-MAR-2001 (364)

Remark: Report of intentional caffeine posiing in a 5-week-old boy. Initial symptoms were agitation and tachycardia. Child´s serum level of 117 µg/ml correspondes to a potential ingestion 600 mg, 125 mg/kg, of caffeine. After symptomatic treatment the child was discharged on the fifth hospital day.
toxic effects (poisoning)
14-JAN-2002 (365)

Remark: A one-year-old white female ingested appr. two to three grams of caffeine (200-300 mg/kG). The patient survived the ingestion wit a maximum caffeine concentration of 385 µg/ml four hours post ingestion. The child developed ventricular arrhythmias, seizures, metabolic disturbances, and severe pulmonary edema. She survived without apparent long-term sequelae.
toxic effects (poisoning)
01-MAR-2001 (366)

Remark: Case report of caffeine ingestion in a 5-year-old boy. On admission at the hospital he was subcomatose with bilateral mydriasis, generalized muscular hypotonia ans an increase heart rate. Serum caffeine level was 15.5 µg/ml and theobromine 3.5 µg/ml. Clinical condition improved under symptomatic threatment and the child was discharged after 24 h in good health.
toxic effects (poisoning)
01-MAR-2001 (367)

Remark: A case report of a 16 year old male who ingested an estimated 6-8 grams of caffeine is described. The patient showed adverse effects including hypokalemia, elevated blood glucose, tachcardia, bigeminy and agitation, respiratory alkalosis and chest pain was also observed. Three serum caffeine levels were analyzed and an abnormally long elimination half-life time of approximately 16 hours was calculated.
toxic effects (poisoning)
14-MAR-2001 (368)

Remark: Case report of an 22-year-old female with cardiac arrest and death after ingestion of diet pills containing caffeine.
Serum caffeine concentration was 1,560 µg/ml.
toxic effects (poisoning)
01-MAR-2001 (369)

Remark: Case report of a 58-year-old woman who ingested more than 35 g of caffeine in a suicide attempt. The patient showed multiple dysrhythmias and was successfully treatet with the ß1-blocker esmolol.
toxic effects (poisoning)
01-MAR-2001 (370)

Remark: Report of case of overdosing of caffeine (7.5 g of caffeine over the previous three days in the form of nutrition tablets).

The 28 year old man complained of tiredness and nausea and during a strenuous circuit training he collapsed and was witnessed to have a grand mal seizure lasting 15 minutes. Caffeine serum concentrations was 12.3 mg/l. After three days on the ward and no further fits the patient was discharged with outpatient follow up. He remains seizure-free and has normal renal function.
toxic effects (poisoning)
01-MAR-2001 (371)

Remark: Report of a case of caffeine-induced fever. Skin prick test were negative. Single-blind oral challenges with caffeine were positive, reproducing chills, high-grade fever, myalgia, and cephalea.
toxic effects (fever)
14-JAN-2002 (372)

Remark: The effect of caffeine consumption on mortality was evaluated in a historical cohort study of 10,064 diagnosed hypertensive individuals participating in the Hypertension Detection and Follow-up Program from 1973 to 1979. No evidence was found supporting an association between increased level of caffeine consumption and increased all-cause mortality or cardiovascular disease mortality during the following four years.
toxic effects (CVD)
15-FEB-2001 (373)

Remark: In a prospective study over 4 years in a base population of 1,980 men to examine association to several social and dietary effects. 88 cases of coronary heart disease have developed. This approximates one case per 100 men. No relation was encountered between body weight, mean blood sugar levels, lipoprotein lipase levels, or diet (other than coffee). Data for a total of 1,108 the men during the last 9 months of the first year showed a significant correlation.
toxic effects (CHD)
15-FEB-2001 (374)

Remark: 276 patients with acute myocardial infarction has been compared with 1,104 controls to assess association to coffe intake. patients with acute myocardial infarction were found to drink appreciably more coffee than the matched controls.
toxic effects (CHD)
15-FEB-2001 (375)

Remark: A positive association between coffee consumption and acute myocardial infarction was confirmed in a survey of 12,759 hospital patients, including 440 with a acute myocardial infarction. As compared with those who drink no coffee, the risk ofs of infarction among those drinking one to five and six or more cups of coffee per day are estimated to be

increased by 60 and 120 per cent, respectively.
toxic effects (CHD)
15-FEB-2001 (376)

Remark: Association of coffee intake and coronary heart disease was examined in a series of 649 patients who died of coronary heart disease and an equal number of controls. The RR associtaed with coffee drinking was 1.1 (95% CI 0.8-1.6).
toxic effects (CHD)
14-MAR-2001 (377)

Remark: The effect of caffeine-containing coffee on the risk of myocardial infarction was investigated in 487 female patients with first infarction and 980 controls. Overall and in various subgroups, coffee drinking and myocardial infarction were weakly and not significantly associated: the overall estimated RR for women drinking at least five cups daily, compared with women drinking none, was 1.4 (95% CI 1.0-1.9) after control for all identified potential confounding factors.
toxic effects (CHD)
14-MAR-2001 (378)

Remark: Relationship between coffee consumption and risk of coronary
heart disease among women was examined in a prospective cohort study with a total of 85,747 women. During ten years of follow-up 712 cases of CHD were documented. No evidence for any positive association between coffee consumption and risk of subsequent CHD was found.
toxic effects (CHD)
14-MAR-2001 (379)

Remark: The relation of coffee and alcohol consumption to the risk of coronary heart disease during a six-year period was examined in a cohort of 7,705 Japanese men. The analysis was based on 294 new cases of coronary heart disease. There was a positive association between coffee intake and risk, but it became insignificant when cigarette smoking was taken into account. There was a strong negative association between moderate alcohol consumption and the risk of nonfatal myocardial infarction and death from coronary heart disease.
toxic effects (CHD)
14-MAR-2001 (380)

Remark: A prevalence survey was conducted during 1960 to 1962, and the study population was reexamined between 1967 and 1969. During this second study of 2,530 adults attended and were asked concerning coffee consumption. The cohort was followed up annually for 4.5 years with questionnaires. A total of 339 deaths occurred, 130 attributed to cardiovascular and cerebrovascular causes. Total mortality showed no asociation with coffee usage. Death of coronary heart disease showed no significant difference between high and low coffee consumers.
toxic effects (CHD)

14-MAR-2001 (381)

Remark: In this cohort study, 16,911 men who had completed a mailed dietary questionnaire were followed for 11.5 years with 721 deaths reported from ischemic heart disease (IHD). Although no association was found between coffee consumption and mortality from IHD, a negative association between coffee consumption and mortality from diseases other than IHD was found. This negative association, found exclusively in the first four years of follow-up, was observed in deaths from digestive diseases, other than malignancies, and paralysis agitans. The negative association appeared to reflect a reduction in coffee consumption.
toxic effects (CHD)

14-MAR-2001 (382)

Remark: Relation between coffee consumption, coronary heart disease,
and mortality in two prospective studies were examined. In the observational study a negative correlation for blood pressure and coffee consumption was found. Coffee consumption was not related to total mortality or CHD (when smoking habits was taken into account). In the Primary Preventive Trial a weak negative association between coffee consumption and blood pressure and a significant positive correlation between coffee consumption and serum cholesterol was found.
toxic effects (CHD)

14-MAR-2001 (383)

Remark: The relation of coffee consumption with risk of myocardial infartion and stroke was examined in a prospective study with 45,589 men. During two years of follow-up observation, 221 participants had a nonfatal myocardial infarction or died of coronary heart disease, 136 underwent coronary-artery surgery or angioplasty, and 54 had a stroke.
Total coffee consumption was not associated with an increased risk of coronary heart disease or stroke.
toxic effects (CHD)

14-MAR-2001 (384)

Remark: The effect of coffee consumption on the incidence of coronary heart disease was studied prospectively in a population sample of 6,765 men. During a 7.1-year follow-up there were 230 non-fatal myocardial infarctions, 169 coronary deaths and 478 deaths from all causes. Among men who were smokers at baselne there was no relationship between either non-fatal MI or death from CHD, and coffee consumption. Among non-smokers, a weak but far from significant trend towards an increasing incidence of CHD in heavy consumers of coffee was observed. There was an inverse relationship between mortality from all causes and coffee consumption.
toxic effects (CHD)

14-MAR-2001 (385)

Remark: In a prospective study with a 21 year follow up coronary heart disease mortality and coffee consumption was examined in a total of 5,766 men. Altogether 625 men died from coronary heart disease. No clear evidence of an overall relationship between coffee use and coronary heart disease mortality was found, although the small number of men consuming high amounts of coffee may have limited the power of the study to detect a statistically robust effect. toxic effects (CHD)

01-MAR-2001 (386)

Remark: Eight case-control and 15 cohort studies were analyses to examine the association between coffe drinking and risk of coronary heart disease. The pooled case-control odds ration (for the effect of drinking five cups of coffee/day versus none) was 1.63 (95% CI 1.5-1.78). The pooled cohort study relative risk was 1.05 (95% CI 0.99-1.12). The discrepancy between the pooled case-control and cohort study results could not be attributed to differences in the end points chosen, period of study, or to confounding by smoking status or sex.
toxic effects (CHD)
15-FEB-2001 (387)

Remark: Association of caffeinated and decaffeinated, and tea with myocardial infarction was investigated in a study of 340 cases and community-matched controls. The OR for drinking >=4 cups/day of caffeinated coffee versus drinking <=1 cups/week was 0.84 (95% CI 0.49-1.42). For tea, the OR for drinking >=1 caup/day versus nondrinkers was 0.56 (95% CI 0.35-0.90).
toxic effects (CHD)
16-FEB-2001 (388)

Remark: Single oral dose of caffeine on plasma renin activity, catecholamines and cardiovascular control was studied in nine healthy subjects. Caffeine (250 mg or placebo) increased plasma renin activity by 57%, plasma norepinephrine by 75% and plasma epinephrine by 207%. Mean blood pressure rose 14/10 mmHg one hour after caffeine ingestion. Heart rate showed a slight fall and then a rise.
toxic effects (RR)
15-FEB-2001 (389)

Remark: In a double-blind crossover trial the effect of 4 week daily ingestion of 504 mg caffeine (8 cups) vs. 8 cups of decaffeinated coffee was studied in 10 healthy volunteers. Caffeine immediately led to a significant increase in mean blood pressure (+3 and +5 mmHg respectively). The increase existed only in the first 3 to 5 days of intake. On day 5 after ingestion and thereafter no significant increase in catecholamine excretion was observed.
toxic effects (RR)
27-FEB-2001 (390)

Remark: The association between coffee intake and blood lipids and blood pressure was studied in 14,168 men and 14,859 women. Serum cholesterol increased linearly with increasing coffee consumption (8% for men and 10% for women). Triglycerides showed a negative association with coffee consumption. Drinking 1 cup of coffee or more, a significantly negative association between both systolic and diastolic blood pressure and number of cups was found.
toxic effects (RR)
14-MAR-2001 (391)

Remark: Relationship between dietary variables and blood pressue in

men randomly assigned into the Multiple Risk Factor Intervention Trial was investigated. There was a significant inverse relation of caffeine intake to both systolic and diatolic blood pressure for all participants.
toxic effects (RR)

14-MAR-2001 (392)

Remark: The relation between habitual coffee consumption and blood pressure was studied in 500 subjects. Blood pressure levels showed a significant decrease with increasing coffee consumption. Systolic blood pressure and diastolic blood pressure were respectively 130.4 mmHg and 81.5 mmHg for non-coffee drinkers, 129.4 and 82.2 mmHg for 1 cup per day, 128.4 and 81.4 mmHg for 2-3 cups per day, and 124.1 and 78.7 mmHg for more than 6 cups of coffee daily.
toxic effects (RR)

14-MAR-2001 (393)

Remark: Association between coffee consumption, tobacco consumption,
and blood pressure was examined in a cross-sectional study of 1,098 men and 393 women. Systolic blood pressure was negatively and significantly correlated with cigarette smoking. Diastolic blood pressure was positively and significantly associated with coffee consumption and negatively and significantly with cigarette consumption.
toxic effects (RR)

31-AUG-2001 (394)

Remark: The possible link between coffee drinking and blood pressure was studied in a cross-sectional epidemiologic survey of 6,321 subjects. Systolic and diastolic blood pressue levels were higher among the 5,430 coffee drinkers than among the 891 nondrinkers. Blood pressure levels increased gradually from the non-coffee consumption category (125.6 mmHg) to the highest consumption category (>=5 cups/day) (128.1 mmHg) for systolic blood pressure. The positive association was significant for systolic blood pressure.
toxic effects (RR)

31-AUG-2001 (395)

Remark: Coffee consumption was determined at the fourth biennial examination in the Framingham Study to ascertain its relation to cardiovascular disease. The association between coffe and other risk factors, including cigarette smoking, was also investigated over the 12-year follow-up period. Coffee drinking was studied in relation to total coronary heart disease, angina pectoris, myocardial infarction, sudden death, and death from all causes. A statistically significant increase in risk with increasing coffee consumption was observed only in the categorie "death from all causes", which could be accounted for by the association between coffee consumption and cigarette smoking.
toxic effects (RR)

13-MAR-2001 (396)

Remark: A screening of initial examinations in 72,101 subjects performed relating coffee consumption to blood pressue showed essentially the same distribution in all coffee-drinking categories.

No specific relation between daily coffee consumption and blood pressure elevation was seen.
toxic effects (RR)

14-MAR-2001 (397)

Remark: 21 healthy, nonsmoking, habitual coffee drinkers received daily doses of 100 mg and 500 mg of caffeine on 2 days in a crossover design. Ambulatory monitoring was conducted for 6 to 9 hours during normal workday acitivites. The average workday blood pressure and heart rate were significantly higher when the higher dose of caffeine was consumed. Dose-related differences were 4 mm Hg for systolic and 3 mm HG for diastolic blood pressure, and were 3 bpm for heart rate.
toxic effects (RR)

14-MAR-2001 (398)

Remark: Review on effects of caffeine on blood pressure and heart rate: results from epidemiological studies are inconsistent.

Experimental laboratory studies have generally found that caffeine produces acute rises in systolic and diastolic BP that are additive to any stress-induced increases. Synergic effects which might pose a more serious risk are rarely found. Heart rate data are less consistent, possibly due to the different ways HR is measured. Tolerance to the cardiovascular effects of caffeine has reliably been reported; however, overnight abstinence may be sufficient to negate tolerance effects to most levels of caffeine ingestion in typical users. Though caffeine drinkers may exhibit acute increases in BP, the long-term effects appear to be minimal. However, persons at risk for hypertension may be more vulnerable to the BP effects of caffeine.
toxic effects (RR)

14-MAR-2001 (399)

Remark: toxic effects (RR)
Twenty-three hypertensive patients who refrained from caffeine for 2 to 3 weeks were given 250 mg oral caffeine powder dissolved in water. A significant increase in systolic and diastolic blood pressure occurred in 13 subjects. A statistically significant decrease in heart rate was seen during first hour of caffeine intake. Marked diuresis and natriuresis were observed for the first 6 hours after intake. Renin and endothelin levels were unchanged.
Although chronic studies point to development of tolerance to long-term caffeine ingestion, acute studies showed

immediate effects.
27-FEB-2001 (400)

Remark: Psychomotor stress plus caffeine (3.3 mg/kg bw) was investigated in 24 men with borderline hypertension and 24 controls. BH men had modestly larger BP increases to the task and showed a greater combined effect of caffeine plus the task (+15/+11 mmHG) than controls (+10/+6 mmHg).
toxic effects (RR)
01-MAR-2001 (401) (402)

Remark: A population survey of 7,311 men was done to examine the association of ventricular premature beats with caffeine intake. A significant relationship with ventricular premature beats was found for the average daily number of tea or coffee consumed. Heavy coffee consumption (>= 9 cups/day) was associated with more than twice the likelihood compared to light cosnumption (<= 2 cups/d) or abstinence.
toxic effects (arrhythmia)

14-MAR-2001 (403)

Remark: Prevailing cardiac rhythm an rate, the prevalence and frequency of ventricular dysrhythmia, and Q-T intervals were compared in two populations over an initial 24-hour caffeine-free period and a subsequent 24-hour period in which caffeine was ingested in a dosage of 1 mg/kg of body weight at intervals of one elimination half-time during waking hours. Group 1 was composed of 18 clinically normal subjects; group 2 was 18 subjects with frequent ventricular ectopic beats and no (n=16) or minor (n=2) cardiac disease. The data suggest that in the given doses and in the absence of major underlying cardiac disease, caffeine does not significantly affect prevailing cardiac ryhthm or rate, nor the mean rate of ventricular repolarization. The data also suggest, that caffeine can have a ventricular dysrhythmogenic effect, and although the clinical significance is still not completely certain, it seems reasonable to use it with caution in patients who may be at increased risk from ventricular dysrhythmia.
toxic effects (arrhythmia)

28-JUN-2001 (404)

Remark: The effect of chronic caffeine adminsitration (250 mg/d) on blood pressure, heart rate, plasma epinephrine, plasma norepinephrine, plasma renin activity, and urinary catecholamines were studied in 18 health subjects. Near complete tolerance, in terms of both humoral and hemodynamic variables, developed over the first 1-4 days of caffeine.

No long-term effects of caffeine on blood pressure, heart rate, plasma renin activity, plasma catecholamines, or urinary catecholamines were found. Discontinuation of caffeine ingestion after 7 d of adminsitration did not result in a detectable withdrawl phenomenon.
toxic effects (arrhythmia)

14-MAR-2001 (405)

Remark: Caffeine (300 mg) was administered to each of 70 patients a mean of 7 days after the onset of acute myocardial infarction to determine its effects on ventricular arrhythmias. Caffeine increased mean blood pressure from 116 to a maximum of 125 at 4 hours. Plasma epinephrine increased from 58 to a maximum 88 pg/ml e hours after caffeine ingestion. No increase in occurence or severity of

ventricular arrhythmias were observed.
toxic effects (arrhythmia)
15-FEB-2001 (406)

Remark: The role of caffeine restriction in patients with symptomatic idiopathic ventricular premature beats was assessed in 13 patients. The intervention achieved signifiant alterations in serum caffeine concentrations which correlated with coffee consumption. No significant changes in palpitation scores or ventricular premature beat frequencies during the intervention weeks and no significant correaltions were found between these variables and caffeine concentrations.
toxic effects (arrhythmia)
20-FEB-2001 (407)

Remark: review: acutely administered caffeine modestly increases blood pressure, plasma catecholamine levels, plasma renin activity, serum free fatty acid levels, urine production, and gastric acid secretion. Chronic caffeine consumption has no effect on blood pressure, plasma catecholamine levels, plasma renin activity, serum cholesterol concentration, blood glucose levels, or urine production. Caffeine does not seem to be associated with myocardial infarction; lower urinary tract, reanl, or pancreatic cancer, teratogenicity, or fibrocystic breast disease. The role of caffeine in cardiac arrhythmias or gastric or duodenal ulcers remains uncertain.
toxic effects (arrhythmia, review)
14-MAR-2001 (408)

Remark: The association between coffee consumption and stroke was examined in men at high risk for cardiovascular disease. Subjects were 499 hypertensive men. In the cours of follow-up, 76 men developed stroke. Risk of thromboembolic stroke increased significantly with increases in coffee consumption. No relationship were observed with hemorrhagic stroke. When adjusted for other factors, the risk of thromboembolic stroke was more than doubled for men who consumed three cups of coffee per day as compared to nondrinkers of coffee (RR 2.1, 95% CI 1.2-3.7).
toxic effects (stroke)
15-FEB-2001 (409)

Remark: The effect of decaffeinated versus regular coffee (5 cups a day for 6 weeks) on serum lipids was examined in 45 healthy volunteers in a randomized double-blind crossover trial. Differences between the effects of decaffeinated and regular coffee on blood lipids were essentially zero; the effect on total serum cholesterol was 0.01 (+- 0.36 mmol/l), on high density lipoprotein cholesterol was 0.01 (+- 0.11 mmol/l), and on triglycerides was 0.03 (+- 0.29 mmol/l).
toxic effects (lipids)
14-MAR-2001 (410)

Remark: 181 men consumed a standard caffeinated coffee for 2 months

followed by randomization to continue caffeinated coffee, change to decaffeinated coffee or no coffee for 2 months. Plasma low-density lipoproatein (LDL) cholesterol and apolipoprotein B concentrations increased significantly in the group that changed to decaffeinated coffee. Discontinuation of caffeinated revealed no change. This findings suggest that a coffee component other than caffeine is responsible for LDL cholesterol, apolipoprotein B, and lipase activity changes reported in this investigation.
toxic effects (lipids)

15-FEB-2001 (411)

Remark: Thirteen normal men participated in a randomized, doube-blind test of the effects of caffeine (600 mg/day or placebo) on plasma lipids, lipoproteins, apolipoproteins, fat tolerance, and post-heparin lipases. There was no significant differences between the placebo and caffeine intake, resp., in total cholesterol (190 vs. 191 mg/dl), LDL-cholesterol (123 vs. 119 mg/dl), apoB (99 vs. 98 mg/dl), HDL-cholesterol (49 vs. 51 mg/dl), HDL2-cholesterol (19 vs. 20 mg/dl), or triglycerides (89 vs. 103 mg/dl).
toxic effects (lipids)

15-FEB-2001 (412)

Remark: A meta-analysis of randomized controlled clincial studies on coffee consumption and serum lipids was performd of 14 published trials. A dose-response relation between coffee consumption and both total cholesterol and LDL cholesterol was identified ($p < 0.01$). Increases in serum lipids were greater in studies of patients with hyperlipidemia and in trials of caffeinated or boiled coffee. Trials using filtered coffee demonstrated very little increase in serum cholesterol. Consumption of unfiltered, but not boiled coffee increases serum levels of total and LDL cholesterol.
toxic effects (lipids)

14-MAR-2001 (413)

Remark: Effect of 200 mg caffeine peroral on glucose tolerance was investigated in 30 healthy subjects. Caffeine intake induces an insulin independent rise in blood glucose levels.
toxic effects (glucose)

01-MAR-2001 (414)

Remark: The association between smoking, caffeine and alcohol intake and the risk of duodenal ulcer was examined in a prospective cohort of 47,806 men using a mailed baseline questionnaire in 1986, with follow-up ever 2 years through 1992. The results indicate that smoking is not associated with a substantial increase in risk of duodenal ulcer, nor is high intake of alcohol and caffeine.
toxic effects (gastrointestinal)

15-FEB-2001 (415)

Remark: Effect of caffeine intake on calcium excretion was examined in 17 young women. After both abstention and adaptation

weeks, addition of caffeine significantly increased excretion from 2.9 to 6.7 mg Ca/hour. Caffeine similarly affected urinary magnesium and sodium. Young women chronically consuming 300 mg caffeine/day contiuned to excrete increased calcium, magnesium and sodium after a caffeine callenge when compared to caffeine-free week.
toxic effects (calcium)

14-MAR-2001 (416)

Remark: Total urinary three hour excretion of calcium, magnesium and sodium was increased significantly in twelve female subjects after intake of 150 or 300 mg caffeine peroral. Total urine volume correlated significantly with dose of caffeine per body weight when 300 mg of caffeine was consumed.
toxic effects (calcium)

31-AUG-2001 (417)

Remark: toxic effects (calcium)
Urinary calcium excretion was measured in nine female fasting subjects who each randomyl ingested four treatments on nonconcurrent mornings; no drug, caffeine (5 mg (kg bw), ASS 650 mg, or caffeine plus ASS. Urinary calcium excretion rose with caffeine treatment (0.49 mmol/mmol creat. vs. 0.23 mmol/mmol creat.). ASS caused a significant reduction in urinary calcium to 0.13 mmol/mmol creat.; when it was combined with caffeine, caffeine-induced calcium excretion fell significantly to 0.35 mmol/mmol creat. Sodium excretion tended to reflect calcium excretion.

01-MAR-2001 (418)

Remark: Relationships among nutrition, hormone concentrations, and bone density of the spine in 27 vegetarian and 37 nonvegetarian premenopausal women were evaluated. Caffeine intake in both groups had a positive effect on urinary calcium excretion, but no association was observed between bone density and caffeine intake.
toxic effects (calcium)

01-MAR-2001 (419)

Remark: The influence of coffee drinking as a possible risk factor for loss of bone mass was assessed in a cohort of 619 70-year-old men and women. Coffee drinking was not a contributory independent risk factor for loss of bone mass and fractures in this population.
toxic effects (calcium)

14-MAR-2001 (420)

Remark: The effect of caffeine consumption on rates of change in bone mineral density were examined in 205 healthy, nonsmoking, postmenopausal women. Among women consuming less calcium (< 800 mg/d), those with highest caffeine intakes (>450 mg/d) had significantly more bone loss than did women consuming less caffeine (0-171 and 182-419 mg/d).

toxic effects (calcium)

01-MAR-2001 (421)

Remark: In a case-control study (102 hip fracture, 154 wrist fracture, and 277 controls) the effect of diet on the risk of postmenopausal fracture of the hip and wrist was examined. Higher dietary calcium intake only slightly increased the risk of hip fracture; however, it was associated with a significantly decreased risk for frature of the wrist, at the level >= 1 g/day. Coffee and tea consumption appeared to be unrelated to fracture risk. toxic effects (calcium)

01-MAR-2001 (422)

Remark: Bone density of both hips and the total body was measured in 138 healthy postmenopausal women aged 55-70 to examine effect of caffeine intake and bone loss. The habitual dietary caffeine intake of this cohort of 138 postmenopausal women ranged from 0-1400 mg/d and was not associated with total body or hip bone density measurements.
toxic effects (calcium)

01-MAR-2001 (423)

Remark: The effect of caffeine on hip fracture in 3,170 individuals attending the 12th (197-1973) Framingham Study examination was examined. For intake of 3-4 cups of coffee/tea per day, the RR of fracture was not significantly elevated compared with less intake. Consumption of >=5 cups per day significantly increased the risk of fracture.
toxic effects (calcium)

14-MAR-2001 (424)

Remark: A positive relation between caffeine intake and risk of hip but not forearm fracture was found in 593 forearm and 65 hip fractures occurred in asociation with mild to moderate trauma. After potential risk factors were controlled for, the RR of hip fracture for women in the top quintile of caffeine consumption was 2.95 (95 % CI 1.18-7.28).
toxic effects (calcium)

14-MAR-2001 (425)

Remark: The effect of nutrition and dietary caffeine consumption and physical activity on bone gain in women during the third decade of life was investigated in a longitudinal, descriptive study of 145 healthy women. The median rates of bone gain were 5.9% for spine bone mineral content, 6.8% for spine bone mineral density and 12.5% for total body bone mineral. In a multiple regression analysis the significant predictors of the rate of gaine were age (-), activity (+), calcium intake (+) and protein intake (-). Caffeine consumption was not associated with significant reduction in rates of bone gain.
toxic effects (calcium)

14-MAR-2001 (426)

Remark: The association between dietary caffeine consumption and bone mineral gain and hip bone density was studied in 81 females aged 12 to 18 years. There were no significant differences among the three caffeine intake groups (<25 mg, 25-50 mg, >50 mg) for total body bone mineral gain or hip bone density.
toxic effects (calcium)

01-MAR-2001 (427)

Remark: The cross-sectional association between caffeine intake and

endogenous androgens, estrogens, and sex hormone-binding globulin was examined in 728 postmenopausal women. Significant inverse associations were noted between caffeine intake and bioavailable testoterone.

At high doses (more than two cups of coffee a day), caffeine intake was positively associated with plasma estrone. Sex hormone-binding globulin levels were positively associated with increasing caffeine intake.
toxic effects (hormone)
27-AUG-2001 (428)

Remark: The most frequently reported withdrawl symptom is headache. Other symptoms, in roughly decreasing order of prominence, are: drowiness, increased work difficulty, decreased feelings of well-being/contentment, decreased sociability/friendliness/talkativeness, flu-like feelings, and blurred vision.
Caffeine has two defining characteristics of prototypic drugs of abuse. In as much as the relative abuse liability of a drug can be consiered to be multiplicative function of the degree of reinforcing effect and the degree of adverse effects, the modest reinforcing effect and modest adverse effects documented would suggest a low abuse potential.
toxic effects (tolerance and withdrawl, review)
15-FEB-2001 (429) (430)

Remark: Thirty-two healthy subjects with histories of moderate caffeine consumption abstained from dietary caffeine throughout the study. Subjects received either caffeine (300 mg t.i.d.) or placebo for 18 consecutive days. The study documented tolerance development to the subjective effects of caffeine: after chronic dosing, administration of caffeine produced significant subjective effects in the chronic placebo group but not in the chronic caffeine group.
The study also provided indirect evidence for tolerance development: during chronic dosing, the chronic caffeine and placebo did not differ meaningfully on ratings of mood and sunjective effect.
toxic effects (tolerance and withdrawl)
31-AUG-2001 (431)

Remark: Tolerance to the diuretic effect of caffeine intake was examined in three healthy volunteers. Distinct evidence of tolerance to the diuretic effect of caffeine was present. Minimal doses of caffeine usually shortened reaction time and dicrimination time in individuals who were tolerant to the diuretic effect. Minimal doses of caffeine usually lengthened reaction time and discrimination time in individuals who were not tolerant to the diuretic effect.
toxic effects (tolerance and withdrawl)
15-FEB-2001 (432)

Remark: Pharmacokinetics and effect on mood and alertness of a single oral dose of 600 mg of a slow release caffeine in 120 healthy subjects was investigated. The dose was well tolerated due this relative low plasma Cmax (10.37 µg/ml). Between placebo and caffeine intake there were no significant differences for alertness, contendness and sleep quality of the night after treatment.

toxic effects (tolerance and withdrawl)
14-MAR-2001 (433)

Remark: Caffeine withdrawl was examined in 12 caffeine-dependent humans living in a residential laboratory in a 17-day study.
Participants were maintained on caffeine (100 mg 3 times a day), except on days 5-6 and 12-13, when caffeine was replaced by placebo. Caffeine abstinence selectively influenced subjective effects without altering social behavior or performance on tasks assessing memory, vigilance, and psychomotor skills.
toxic effects (tolerance and withdrawl)
01-MAR-2001 (434)

Remark: The effects of short-term caffeine-deprivation on mood, withdrawl symptoms and psychomotor performance were studied in 31 habitual coffee drinkers receiving 250 mg caffeine or placebo. Caffeine deprivation was associated with decreased vigor and increased fatigue and with symptoms including sleepiness and yawing. Blood pressure was lower by 5-6 mmHg.
No changes in psychomotor performance were observed.
toxic effects (tolerance and withdrawl)
01-MAR-2001 (435)

Remark: Thirty normal children completed the single blind, within-subject repeated-measures study with weekly sessions to determine withdrawl effects after cessation of caffeine intake. Subjects were evaluated with self-report measures of symptoms and objective measure of attention, motor performance, processing speed, and memory. During caffeine withdrawl, there was a significant deterioration on response time of a visual continous performance test attention. The deterioration in response time appeared to persist for 1 week.
toxic effects (tolerance and withdrawl)
01-MAR-2001 (436)

Remark: review on caffeine dependence. Caffeine has both positive effects that contribute to widespread consumption of caffeine-containing beverages and adverse unpleasant effects
if doses are increased. Caffeine has weak reinforced properties, but with little or no evidence for upward dose adjustment, possibly because of the adverse effects of higher doses. Withdrawl symptoms, although relatively limited with respect to severity, do occur, and may contribute to maintenance of caffeine use is not associated with incapacitation. The positive stimulatory effects of caffeine appear in large measure to be due to blockade of A2A receptors that stimulate GABAergic neurons of inhibitory pathways to the dopaminergic reward system of the striatum.
However, blockade of striatal A1 receptors may also play a

role.
toxic effects (tolerance and withdrawl, review)
01-MAR-2001 (437)

Remark: toxic effects (tolerance and withdrawl)
Twenty healthy volunteers paricipated a study to investigate whether measurable changes in cerebral blood flow velocities could develop from caffeine use or from its withdrawl.
After 24 h of complete caffeine abstinence 10 suffered from moderate to severe headache with complete recovery within 1 h after caffeine intake. The BFVs in both middle cerebral, both posterior cerebral and basilar arteries were higher following the withdrawl period, reaching statistical significance in the left middle cerebral basilar and both posterior posterior arteries. BFVs decreased significantly within half an hour after caffeine intake in all subjects, and were simmilar to baseline values after 2 hours.
14-MAR-2001 (438)

Remark: Review of medical literature on fibrocystic breast disease and caffeine intake indicated a weak evidence for an association.
toxic effects (benign breast disease, review)
15-FEB-2001 (439)

Remark: Overview: benign breast disease in relation to caffeine and other methylxanthines (case series, intervention in trials and etiological studies).
There is controversy about the role of caffeine in benign fibrocystic breast disease (FDB). Some investigators associate caffeine with FBD, since the substance is a phosphordiesterase inhibitor and increases the cAMP level (which stimulates epithelial proliferation and high levels of which are found in benign breast tissue). Many other authors fail to find a significant correlation between caffeine (or coffee) intake and FBD. Several factors are responsible for the inconsistencies in the results. These factors include unknown precise cause of FBD, variability in diagnosis, difficulties in matching controls and classifying patients, and mixed intake of several methylxanthines. No association was found in a study with biopsy-confirmed controls.
toxic effects (benign breast disease, review)
20-FEB-2001 (331) (440)

Remark: The relation of coffee and tea consumption to fibrocystic disease of the breast and to breast cancer was studied in 451 women hospitalized. A modest, positive association between caffeinated beverage consumption and both diseases was found. However, there was no apparent dose-response effect.
toxic effects (benign breast disease)
15-FEB-2001 (441)

Remark: In a case-control study with 323 women with beningn breast disease and 1,428 controls, no differences were noted in

the coffee and tea consumption patterns of the case and the controls.
toxic effects (benign breast disease)
15-FEB-2001 (442)

Remark: Association of caffeine and fibrocystic breast disease was studied in a retrospective 5-year study of 358 women and a 6-month prospective study of 72 women. More than 70 % of women with histologically proven fibrocystic breast disease show change with breast examinations 6 to 12 months, thus no stable clinical findings in fibrocystic breasts were observed over a long period. Caffeine intake did not change.
In the prospective study 90% of left breasts and 83% of right breasts showed changes in position or number of nodules. All nodules disappeared from 13% of the right breasts and from 17% of the left. In 28 % of left breasts and 39% of right breasts, the nodules disappeared only to reappear during the 6 months. Caffeine consumption increased by 24 mg/d between the first and last examination.
toxic effects (benign breast disease)
14-MAR-2001 (443)

Remark: A dietary case-control study of 854 histologically diagnosed cases of benign breast disease, 755 matched surgical controls, and 723 matched neigborhood controls was conducted. No association between coffee consumption and BBD was found. Analyses by histological type, degree of ductal atypia, age, sex, and ethnic origin, controlling several confounding factors, confirmed the lack of association.
toxic effects (benign breast disease)
16-MAR-2001 (444)

Remark: A case-control study involving 383 cases of biopsy-confirmed
benign proliferative epithelial disorders of the breast and 192 controls whose biopsy did not show epithelial proliferation and 383 unbiopsied community controls to examine the relationship to methylxanthine intake was performed. There was relatively little variation in risk with total methyxanthine intake, or with intake of the xanthine derivates theophylline and caffeine, while the positive association between theobromine intake and risk was observed only when cases were compared with biopsy controls.
toxic effects (benign breast disease)
16-MAR-2001 (445)

Remark: The relationship between methylxanthine consumption and benign breast disease was evaluated in a case-control study of 288 women with histologically confirmed benign breast lumps and 2 groups of control women (285 patients in the hospital for acute conditions apparently unrelated to the consumption of methylxanthine-containing beverages and 291 outpatients). The RR estimates of dysplastic breast lesions

for women who drank 1-2 or 3 or more cups of coffee per day were 4.1 and 6.4, respectively, when the hospital controls were the comparison group and 2.0 and 3.7, respectively, when the outpatient controls were the comparison group.
toxic effects (benign breast disease)
29-MAR-2001 (446)

Remark: A limited number of human population studies analyzed lymphocytes for chromosomal changes in freshly isolated and cultured lymphocytes from individuals consuming caffeinated beverages. It should be noted that the exact quantities of coffee, type of coffee, or caffeine consumed are not reported in these studies. Thus it is possible that compounds other than caffeine elicited the described results. A study reported that the percentage of human lymphocytes cultured from healthy normal males with chromosomal aberrations corresponded to the amount of
coffee
consumed per day. Those individuals consuming greater than for cups coffee per day had significantly higher 3.9 vs. 2.6) aberrations than those consuming one to four cups per day. Another study indicated that there was a positive relationship between coffee consumption and the number of SCE in human lymphocytes cultured from 30 nonsmoking and smoking healthy normal male blood donors. In a different study those smoking mothers who consumed >14 caffeine-containing beverages per week exhibited a significantly higher amount of a DNA adduct in humanplacental DNA. In another study cytogenetic damage, as indicated by the incidence of micronucleated erythrocytes, was statistically increased twofold in splenectomized individuals who consumed five cups of caffeinated coffee and tea.
mutagenicity (review)
01-MAR-2001 (447)

Remark: Based on the results of mutagenicity tests (in vitro and in vivo) with different test systems, the authors concluded that the changes of coffee and caffeine consumption in moderate to normal amounts to induce mutagenic effects in humans are almost nonexistent.
mutagenicity (review)
01-MAR-2001 (448)

Remark: mutagenicity
The effect of methylxanthines on chromosomes of human lymphocyte in culture was investigated. Caffeine and the dimethylxanthines cause breakage at 750 µg/ml. No chromosome damage was exhibited by monomethylxanthines.
01-MAR-2001 (449)

Remark: Lymphocytes in culture from human volunteers on a regimen of 800 mg of caffeine daily for one month manifested no significant increase in chromosome damage. The highest level of caffeine in plasma was 30 µg/ml. Multiple exposures of lymphocyte cultures from other untreated donors to this concentration was also without chromosome-

damaging effect.
mutagenicity

14-MAR-2001 (450)

Remark: carcinogenicity (review)
review on kinetics, toxic effects, effects on reproduction, genetic effects, and carcinogenicity: caffeine ia s methylxanthine and occurs naturally in more than 60 plant species throughout the world. It is prepared on an industrial scale by methylation of theobromine. Global per-capita consumption of caffeine from all sources was estimated to be 70 mg per day in 1981-82. Caffeine is consumed in beveages such as coffee, tea, and mate and in soft drinks to which caffeine is added. Coffee is the main source of dietary caffeine consumption. The caffeine content of beverages varies widely. Caffeine is also used in numerous prescription and non-prescription pharmaceutical preparations.
A cohort study with short follow-up period showed no association between caffeine consumption and mortality from cancers at all sites, although there was few deaths on which to base an analysis. Four case-control studies of breast cancer in which an attempt was made to measure methylxanthine intake showed no association. A slight increase in risk was seen in premenopausal women in one study, but in general the relative risks were below unity. One case-control study of bladder cancer showed a weak association with caffeine-consumption. Caffeine and coffee consumption are highly correlated in most of the populations studied; thus it is very difficult to seperate the two exposures in epidemiological studies. It was therefore not possible to evaluate adequately the effect of caffeine per se.
Caffeine intake from pharmaceutical sources has not been related to teratogenic effects in humans. High levels of either coffee or caffeine consumption were related to an increased frequency of low birthweight. On the basis of the available evidence, caffeine consumed in moderate amounts does not cause any persitent increase in blood pressure in normotensive subjects. Whether caffeine consumed in amounts present in coffee or tea causes cardiac arrhythmia in healthy subjeczs or in patients with heart disease remains an open question. One epidemiological study revealed no effect of caffeine (in coffee-drinking subjects) on the sex ratio of their children. In lymphocytes of normal, caffeine-exposed people, chromosomal aberrations were not observed. An increased frequency of micronucleated blood cells was observed in otherwise healthy splenectomized people exposed to caffeine.
Evaluation: There is inadequate evidence for the carcinogenicity in humans of caffeine. Caffeine is not classifiable as to its carcinogenicity to humans.

13-MAR-2001 (331)

Remark: carcinogenicity (review)
review on carcinogenicity: coffee is the main source of dietary caffeine consumption. The caffeine content of

beverages varies widely.
There is limited evidence in humans that coffee drinking is carcinogenic in the urinary bladder. There is evidence suggesting lack of carcinogenicity of coffe drinking in the human female breast and in the large bowel. There is inadequate evidence in humans that coffee drinking is carcinogenic in the pancreas, ovary and other body sites
20-AUG-2001 (451)

Remark: carcinogenicity (review)
review on on coffee and cancer: it was concluded, that in the doses usually consumed by man, coffee does not have any potential genotoxic, mutagenic or carcinogenic effect. There is still some debate on the effect of coffee in the carcinogenesis of the pancreas, colon, bladder and urinary tract.
20-AUG-2001 (452)

Remark: carcinogenicity (all)
The unadjusted RRs showed no association between caffeine consumption and mortality from cancer or any other cause in a study on mortality from cancer at all sites among 10,064 participants in the Hypertension Detection and Follow-up program in the USA.
27-FEB-2001 (453)

Remark: A dietary case-control study based on 818 newly diagnosed breast cancer patients was conducted between 1975 and 1978. The role of coffee and total methylxanthine intake in breast cancer patients was compared to two matched control populations (surgical controls and neighborhood controls). A nonsignificant negative association was found between coffee and/or methylxanthine consumption and breast cancer.
carcinogenicity (breast)
13-FEB-2001 (454)

Remark: carcinogenicity (breast)
Relationship between methylaxanthine consumption and breast cancer using data from a case-control study which included 1,510 cases and 1882 controls identified through a nation-wide breast cancer screening program. No evidence of a positive association between methylxanthine consumption and risk of breast cancer was observed. Particularly in women diagnosed after age of 50 some suggestion of a negative association was found. The results of caffeine alone were similar to those of total methylxanthines.
13-FEB-2001 (455)

Remark: carcinogenicity (breast)
In a population-based case control study including 451 cases and one control mateched to each case, methylxanthine intake was measured by means of self-administered, quantitative food frequency questionnaire. Intake of caffeine was calculated in different coffees and caffeine-containing drinks as well as that of theobromine intake. No increased risk was found in post-menopausal women in association with total caffeine and total

methylxanthine intake. In pre-menopausal women the increased risk at higher levels of intake was not statistically significant and not dose-dependent.

27-FEB-2001 (456)

Remark: A case-control study of diet and breast cancer was carried out in 150 in 1984-1985. 150 case were identified and for each case a hospital and a neighborhood control was matched.
Multivariate analysis (adjusted for known risk factors) showed no effect of caffeine-containing beverages on breast cancer.
carcinogenicity (breast)

27-FEB-2001 (457)

Remark: carcinogenicity (breast, review)
Results from studies on benign breast disease have been inconsistent, with some investigators observing a positive association and others no association. However, all but one of the studies which have examined methylxanthine intake and
malignant breast disease have concluded that methylxanthine do not play a role in the development of this cancer. Although various methodlogies were employed and different populations were evaluated, results were consistently negative.

29-MAR-2001 (458)

Remark: 101 women with brest cancer were were examined to determine whether caffeine or coffee intake influence cell differentiation (well and moderate versus poor) in tumors. Women with moderately to well-differentiated tumors had higher caffeine or coffee intake than women with poorly differentiated tumors.
carcinogenicity (breast)

29-MAR-2001 (459) (460)

Remark: carcinogenicity (breast)
The association of caffeine intake and postmenopausal breast cancer incidence was assessed among 34,338 women aged 55-69 years in 1986 and followed through 1990. Caffeine intake was assessed by food frequency questionnaire. Median caffeine intake was 212 mg/day in women who developed breast cancer (n=580) and 201 mg/day in women who remained free of the disease (p=0.95). There was no apparent association between breast cancer occurence and quintile of caffeine intake, either adjusted for age or for multiple breast cacer risk factors. The same was true for regular coffee and other caffeine-containing foods.

10-AUG-2001 (461)

Remark: A prospective study of breast cancer in 89,494 women in the Nurses´ Health Study who completed a 61-item food frequency questionnaire in 1980 with repeation in 1984 (n=70,999) was conducted. After a 8 years follow-up, 14,39 invasive breast cancers were diagnosed; in the 4 years of follow-up for the

1984 cohort, 666 cases ocurred. No adverse effect of caffeine was observed; the possibility of a weak inverse association was raised.
carcinogenicity (breast)
10-AUG-2001 (462)

Remark: carcinogenicity (breast, review)
Review on nutrition and breast cancer; the epidemiologic evidence donot suggest any substantial increase in breast cancer risk associated with drinking coffee.
27-AUG-2001 (463)

Remark: carcinogenicity (breast)
Relationship between methylaxanthine and breast cancer was investigated in a large case-control studyof 3,234 women. 1,617 patients were selected from among femals residents, ages 20 to 79, who were diagnosed with a primary, incident breast cancer and a equal number of controls. The size of the study allowed the ability to detect very small increases in risk. As with most other studies of breast cancer and methylxanthines, no increased risk was observed for the consumption of coffee or caffeine.
27-AUG-2001 (464)

Remark: carcinogenicity (breast)
Relationship between smoking, alcohol consumption and caffeine consumption and the risk of breast cancer was examined in a case-control study with a total of 755 women with breast cancer diagnosed before the age of 36, each matched with general population control. There was no evidence of a significant association between caffeine consumption and breast cancer risk, and no apparent trend in the amount of caffeine consumed. There was no evidence of a statistically significant difference in breast cancer risk between subjects who had ever smoked as much as one cigarette per day and those who had not. Consumers of 0.1 - 4.9 and 5.0 - 14.9 g alcohol per day generally had non-significantly increased risks compared with never drinkers, but consumers of more than 15 g per day had reduced risks.
27-AUG-2001 (465)

Remark: carcinogenicity (breast)
The relationship between dietary factors and the risk of breast cancer was investigated in a case-control study a total of 107 incident, histologically confirmed cases of breast cancer and 318 controls. Risk for breast cancer and coffee intake was slightly but not statistically significant reduced for moderate and high intake (OR=0.8 and 0.9) and equals unity for low intake.
27-AUG-2001 (466)

Remark: carcinogenicity (breast)
In two case-control studies conducted in Italy, no association between breast cancer and coffee intake was

found. Cases were 5984 women aged 22-74 years; controls were 5504 women aged 15-74 years.
10-AUG-2001 (467)

Remark: carcinogenicity (colorectal)
No effect or a protecting effect of caffeine on the formation of colon tumors was reported in a cohort study. According to the authors, this was coherent with the lack of mutagenicity observed in Ames tests.
13-FEB-2001 (468)

Remark: carcinogenicity (colorectal)
The combined results from 12 case-control studies showed an inverse association between coffee consumption and risk of colorectal cancer (pooled RR for high vs. low category of coffee consumption (RR) = 0.72, 95% confidence interval (CI) 0.61-0.84); the findings were similar in population-based case-control studies. Five cohort studies did not support an association (pooled RR = 0.97, 95% CI 0.73-1.29). The combined results of all studies were driven largely by the case-control studies, which comprised 85% of the cases (RR = 0.76, 95% CI 0.66-0.89).
13-FEB-2001 (469)

Remark: carcinogenicity (colorectal)
The association between coffee and black tea consumption and the risk of colon and rectal cancer was investigated in a clinical trial cohort (111 cases of colon cancer and 83 of rectal cancer). Coffee was not significantly associated with colon or rectal cancer. A positive association was seen for increased consumption of tea drinking and colon cancer.
14-MAR-2001 (470)

Remark: carcinogenicity (colorectal)
Relationship between social class indicators and colorectal cancer was investigated in a case-control study in 190 patients and 393 controls. The consumption of coffee, tea, and mate was not significantly related to colorectal cancer,
but ORs were below unity (0.9, 95% CI 0.1-1.3 for coffee, 0.9, 95% CI 0.6-1.5 for mate and 0.8, 95% CI 0.6-1.2 for tea).
14-MAR-2001 (471)

Remark: carcinogenicity (colorectal)
The relationship between coffee, decaffeinated coffee and tea intake and risk of cancers of the colon and rectum was investigated in two case-cotrol studies in 2,166 (colon) and 1,364 (rectum) cases and 7,057 controls. Compared with coffee non-drinkers, the risk of colon-cancer was reduced in drinkers of 4 or more cups/day (OR 0.73, 95% CI 0.60-0.89), with a significant trend in risk with dose. No significant association emerged between coffee drinking and risk of rectal cancer (OR 1.00 for drinkers of 4 or more cups/day).
20-FEB-2001 (472)

Remark: A population-based case-control study of bladder cancer including papilloma was performed from 1979-1981 in a total of 371 patients, and a comparable group of 771 controls. The relative risk of bladder cancer in relation to coffee drinking was not statistically significant. A significant association was found between bladder cancer and tea drinking among men, but with no regular trend for increasing consumption. An association was found between risk of bladder cancer and both daily liquid intake and non-cola soft drink. No evidence of an isolated influence of coffee drinking or caffeine intake on bladder cancer is provided.
carcinogenicity (urinary bladder)

13-MAR-2001 (473)

Remark: carcinogenicity (NHL)
In a case-control study conducted in Italy no association between non-Hodgkin's lymphoma and consumption of regular or decaffeinated coffee and tea was found. Cases were 429 subjects aged 17-79 years; controls were 1157 subjects aged 17-79 years.

13-FEB-2001 (474)

Remark: carcinogenicity (lung)
Effect of coffee or tea on lung cancer in male cigarette smokers was examined in a case-control study in 427 lung cancer cases and 428 controls. Coffee drinking had no effect on the lung cacer risk. Black tea consumption decreased the risk (two or more cups a day, RR 0.34, 95% CI 0.14-0.84).

14-MAR-2001 (475)

Remark: carcinogenicity (lung)
Prospective study of coffe drinking , mortality, and cancer incidence in 13,664 Norwegian men and 2,891 women.

Estimated odds ratio (>= 7 versus <= 2 cups of coffee per day) 1.09 (p=0.84)

16-JAN-2002 (476)

Remark: A case-control study was conducted to investigate the dose-relationship betwen coffee and risk of pancreas cancer.
The case-control study was community-based and was carried out in 141 patients with pancreas cancer and 282 controls. The dose-response relationship between coffee (cups/day) and the relative risk of the disease formed a U-shaped curve: in non-smokers and coffee consumption: 1.0 never, 0.3 (0.2-0.7) occasionally, 0.9 (0.5-1.8) 1-2 cups/day, 1.1 (0.4-2.0) 3+ cups/say and for smokers and coffee-consumption: 1.5 (0.8-3.1) never, 0.5 (0.2-1.3) occasionally (0.2-1.3), 0.3 (0.1-0.8) 1-2 cups/day, 2.0 (0.9-4.2) 3+ cups/day.
carcinogenicity (pancreas)

14-MAR-2001 (477)

Remark: In five to six studies a relationship to time to conceive and caffeine and/or coffee have been indicated. There is some evidence that caffeine consumption is associated with miscarriage, but further work is needed to ensure that this is not an artefact due to the increased likelihood of mothers without nausea (and less likely to have reduced coffee intake) being more likely to miscarry. No relationship to major congenital defects was seen. No relationship of preterm delivery and caffeine intake was found. Equivocal evidence of intrauterine growth retaration.
A study of long-term problems in the surving child did not show adverse effects.
reproductive toxicity (review)

13-MAR-2001 (478)

Remark: female subfecundity: results of research on caffeine and subfecundity are equivocal. Two reasonably well controlled cohort studies showed evidence of pronounced and consistant dose-response effects of caffeine on fertility. However, the generalizibility of these findings is unknown. Both studies enrolled select groups of subjects. While the effects of caffeine is not large and it is likely to be obscured in studies of women with other risk factors for delayed conception. Spontaneous abortion: several studies have examined the relation of maternal caffeine use in pregnancy to increased risk of spontaneous abortion, with inconsistent results. At least three earlier studies suggested an association, and a recent retrospective analysis also reported a small but significant trend for increased coffee intake to relate to 1.7% increased risk fo spontaneous abortion. Other studies have reported not finding an asscoiation. Male infertility: caffeine has been hypothesized to influence male fertility because it is deposited in gonadal tissue and excreted into the seminal

fluid. Current data are too sparse to draw conclusions about the effects of caffeine consumption on male infertility.
Teratogenicity: there is virtually no evidence to implicate caffeine in the etiologigy of human congenital malformations. Five of six epidemiologic studies of caffeine
use and malforamtions did not find a significant association. Case reports of malformations in the offspring of high-level users are remarkably rare, despite extensive use of this drug worldwide. Fetal growth: associations between frequent daily coffee drinking and low birth weight were first described in the mid-1970s in two large cohort studies. Considering the limited knowledge of relations between caffeine use and childbearing, disparate results from early research are not surprising, but the the reason for dissimilar results in recent studies that adjusted for relevant confounders is not clear. Preterm delivery was unrelatd to caffeine consumption in all studies of this potential relation, so it is possible that caffeine exerts its influence on low birth weight through intrauterine fetal growth retardation.
reproductive toxicity (review)

16-MAR-2001 (479)

Remark: reproductive toxicity (review)
The effects of caffeine/coffee on fertility, reproduction, lactation, and neonatal development are summarized. There are conflicting reports on the effect of caffeine on human fertility and spontaneous abortion. A teratogenic effect has not been proven. Excessive caffeine exposure (consumption of >7 cups of coffee per day) may result in slight birth weight reduction; moderate coffee consumption has no effect. Caffeine half-life is increased in the neonatal period. Caffeine is excreted in breast milk. Caffeine exposure in utero does not seem to affect long-term neurobehavioural development.
According to the authors, it appears that maternal coffee/caffeine consumption during gestation and/or lactation does not seem to have measurable consequences on the fetus or the newborn, as long as ingested in moderate quantities (<300 mg caffeine per day; corresponding to 2-3 cups of coffee of 2.5-3 l of coke).

15-FEB-2001 (480) (481)

Remark: Caffeine intake from pharmaceutical sources has not been related to teratogenic effects in humans. High levels of either coffee or caffeine consumption were related to an increased frequency of low birth weight. One epidemiological
study revealed no effect of caffeine (in coffee-drinking subjects) on the sex ration of their children.
reproductive toxicity (review)

20-AUG-2001 (331)

Remark: reproductive toxicity (review)
review on reproductive toxicity: the teratogenic potential

of coffee and caffeine-containg beverages was investigated in two cohort and four case-control studies. Two studies (one cohort and one case-control) found significant positive associations between the consumption of caffeine-containg drinks and the risk formalformations. The remaining four studies (one cohort and three case-control), which included the most informative reports, failed to find an association.

Taken together, these studies do not provide evidence of a teratogenic effect of coffee intake.
Eight studies reported an association between decreased birth weight and intake of coffee and caffeine-containing beverages, which was statistically significant in the crude analyses. After correction for confounding variables, including smoking, four studies reported an increased risk among heavy consumers which, however, was not significant, and the other reported a positive association of oly borderline significance. The two remaining studies did not show an association after adjustment for confounding.
Reporting of coffee consumption was usually most complete for the first and seconf trimester, while the greatest impact on birth weight may be vrom consumption during the last trimester. Overall, the data provide an indication that maternal coffee drinking reduces the birth weight of offspring. Of the three studies with adequate design and interpretation, only one showed a clear dose-response relationship.
Information concerning prematurity was insufficient for conclusion to be drawn about an effect of coffee consumption. Ons study provided evidence of a relationship between late spontaneous abortions and modeate to heavy coffee consumption.

20-AUG-2001 (451)

Remark: Observational studies of women have evaluated the association between consumption of caffeine-containing beverages and the risk of delayed conception, spontaneous abortion, prematurity, low birthweight, and congenital malformations. The design and analytic deficiencies of many of these studies limit the inferences based on their findings. The larger and higher quality studies tend to show no relationship between caffeine (or coffee) consumption and pregnancy adversities.
reproductive toxicity (review)

15-FEB-2001 (482)

Remark: Human epidemiologic studies that examine the relationship between caffeine use and congenital abnormalities are not conclusive; however, there is some evidence to suggest a caffeine effect upon fetal growth patterns. Because caffeine drinking is so often associated with the use of other drugs such as tobacco, it is difficult to ascertain which drug has the effect on growth, or if it is a combined effect.
reproductive toxicity (review)

14-MAR-2001 (483)

Remark: evaluation of the reproductive and developmental risks of caffeine
reproductive toxicity (review)
Reliability: (4) not assignable
review, see remark on selection of studies
14-JAN-2002 (484)

Remark: Association between caffeine consumption and decreased fertility was examined in women interviewed during early pregnancy. The women who were heavy coffee drinkers before pregnancy (7 or more cups per day) had, either before or after adjustment, almost a doubled chance of difficulty in becoming pregnant compared with the women who drank little or no coffee (less than 1 cup).
reproduvtive toxicity (delayed conception, infertility)
14-FEB-2001 (485)

Remark: 104 healthy women who had been attempting to become pregnant for three months were interviewed about their use of caffeinated beverages, alcohol, and cigarettes. In their subsequent cycles, women who consumed more than the equivalent of one cup of coffee per day were half as likely to become pregnant, per cycle, as women who drank less. A dose-response effect was present.
reproduvtive toxicity (delayed conception, infertility)
14-FEB-2001 (486)

Remark: In a cross-sectional study the relation between intake of caffeine-containing beverages and time to conception in a population of 1,909 married women was investigated. Intake of caffeine from coffee, tea, and caffeinated soft drinks was associated with an increased risk of a delay of conception of 1 year or more. Compared with no caffeine use,
consumption of 1-150 mg/day of caffeine resulted in an odds ration for delayed conception of 1.39 (95% CI 0.9-2.13), consumption of 151-300 mg/day of caffeine was associated with an odds ration of 1.88 (95% CI 1.13-3.11), and that of over 300 mg/day resulted in an odds ration of 2.24 (95% CI 1.06-4.73), after controlling for last method of birth control used, parity, and number of cigarettes per day.
reproduvtive toxicity (delayed conception, infertility)
07-MAR-2001 (487)

Remark: reproductive toxicity (delayed conception, infertility)
The effect of caffeine intake on fecundability was examined in a retrospective study of 1,430 women. Although smoking per se was associated with a significant increased risk of delayed conception, no effect of high caffeine consumption was observed among women who smoked. Fecundability was reduced among nonsmokers who consumed more than 300 mg caffeine daily.
07-MAR-2001 (488)

Remark: reproduvtive toxicity (delayed conception, infertility)
The effect of caffeine on delayed conception were evaluated

in a European multicenter study in a randomly selected sample of 3187 women (aged 25-44) from 5 countries (Denmark, Germany, Italy, Poland, Spain) between August 1991 and February 1993. Caffeine intake was categorized as 0-100, 101-300, 301-500, and >500 mg. A significantly increased odd ratio (OR) of 1.45 (95% confidence interval (CI) 1.03-2.04) for subfecundicity in the first pregnancy was observed for women consuming more than 500 mg of caffeine per day, the effect being stronger in smokers (OR = 1.56, 95% CI 0.92-2.63) than in non-smokers (OR = 1.38, 95% CI 0.85-2.23). Women in the highest level of consumption (>500 mg/day) had an increase in the time leading to the first pregnancy of 11% (hazard ratio = 0.90, 95% CI 0.78-1.03).
These results were similar for all countries. According to the authors, these results suggested that high levels of caffeine may delay conception among fertile women.

07-MAR-2001 (489)

Remark: In a retrospective cohort study of farm couples was done to determine whether smoking, caffeine, or alcohol use affect fecundability. Information on 2,607 planned pregnancies over previous 30 years were gathered by questionnaires. Caffeine consumption of 100 mg or less versus more than 100 mg in women and men was not associated with fecundability.
reproduvtive toxicity (delayed conception, infertility)

07-MAR-2001 (490)

Remark: reproduvtive toxicity (delayed conception, infertility)
The association between time to conceive reported by 2,817 fertile women who had recently had a liveborn child and consumption of coffee, tea, and caffeinated beverages was investigated. No evidence for an adverse effect of caffeine was found. For levels of consumption ranging from less than one cup of coffee per week (501 mg caffeine per month) to more than two cups of coffee per day (7000 mg caffeine per month), the average time to conceive was similar.

14-MAR-2001 (491)

Remark: A population-based survey of life-style factors and subfecundity (prolonged time to pregnancy) was conducted between 1984 and 1987. 11,888 women filled out a questionnaire in the last trimester of pregnancy (an 86% response). No association was found between subfecundity and consumption of hot caffeinated beverages. For women who smoked and also consumed coffee a statistically significant association was seen (OR 1.35, 95% confidence interval 1.02-1.48).
reproduvtive toxicity (delayed conception, infertility)

13-MAR-2001 (492)

Remark: reproduvtive toxicity (delayed conception, infertility)
To examine the effects of alcohol and caffeine on conception a prospective observational study was done in 124 women, who provided daily urine samples for measurement of steroid hormones and hCG. There was a >50% reduction in the probability of conception during a menstrual cycle

during which participants consumed alcohol. Caffeine did not independently affect the probability of conception.
07-MAR-2001 (493)

Remark: Independent and combined effects of smoking and caffeine intake on the probability of conception was examined in a total of 430 couples. At enrollment and in six cycles of follow-up, both partner filled out a questionnaire on different factors including smoking habits and their intake of caffeine. Compared to nonsmoking women with caffeine intake less than 300 mg/d, nonsmoking women who consumed 300 to 700 mg/d caffeine had a fecundability odds ratio (FR) of 0.88 (95% CI 0.6-1.31), whereas women with higher caffeine intake had a FR of 0.63 (95 % CI 0.25-1.60). No dose-response relationship was found among smokers. Among males, the same decline in point estimates of the FR was present.
reproduvtive toxicity (delayed conception, infertility)
07-MAR-2001 (494)

Remark: Caffeine intake and delay to conception was investigated in 1,050 women with primary infertility and 3,833 women who had recently given birth during the period 1981-1983. A significant increase in the risk of infertility due to tubal disease or endometriosis was observed for the upper levels of caffeine intake, indicating a threshold effect. For tubal infertility, a relative risk of 1.5 (95% CI 1.1-2.0) was found in women who consumed more than 7 g of caffeine per month as compared with those who consumed 3 g or less per month. For endometriosis, the RR was 1.9 (95 % CI 1.2-2.9) in women who consumed 5.1-7 g/month and 1.6 (95% CI 1.1-2.4) in those with intake of more than 7 g/month.
reproduvtive toxicity (delayed conception, infertility)
14-MAR-2001 (495)

Remark: reproduvtive toxicity (delayed conception, infertility)
Two hundred and ten volunteer members of a medical program who were trying to conceive were followed for 12 months or until the month after they became aware they were pregnant. Mean total caffeine intake was 610 mg weekly. There was no significant decrease in fertility associated with total caffeine, coffee, decaffeinated coffee, or caffeinated soda for either moderate or high consumption.
14-MAR-2001 (496)

Remark: reproduvtive toxicity (delayed conception, infertility)
Times to conception for different levels of daily coffee intake were examined in 3,010 women. For all 3,010 women the median time to conception was 2.47 months. Times to conception were longest for the 129 women who drank four or more cups of coffee per day. Times for those drinking 3, 2, 1, or no cups of coffee were similar.
13-MAR-2001 (497)

Remark: Effects of smoking, alcohol, and caffeine consumption and

socioeconimic factors and psychosocial stress on birth weight was examine in a prospective population study in a group of 1,513 women. Smoking was the most important single factor (5% reduction in corrected birth weight). Passive smoking was not a significant factor (0.5% reduction). After smoking was controlled for, alcohol had an effect only in smokers and the effects of caffeine became nonsignificant.
Only for the socioeconomic and stress factors significantly reduced birth weight and these effects became nonsignificant after smoking was controlled for.
reproductive toxicity (low birth weight)

13-FEB-2001 (498)

Remark: 11,858 pregnant women out of 13,815 responded to a mailed questionnaire on eating and drinking habits during pregnancy. Data on pregnancy were recorded from medical files. Maternal coffee consumption of four cups a day or more was associated with a moderate decrease in birthweight, especially among smokers. The association between coffee consumption and preterm births or congenital malformations were very weak. No unexposed group was available in the study, and the exposure was probably misclassified to some extend. Information on potential important time-specific exposure are missing and most measures were also based upon prevalence recording at birth.
reproductive toxicity (low birth weight)

14-MAR-2001 (499)

Remark: A population-based study in 7,025 women was done to assess effect of caffeine intake during pregnancy on intrauterine retardation, low birth weight, and preterm birth. Caffeine consumption was associated with an increased risk of intrauterine growth retardation. For women whose average daily caffeine consumption was 0-10, 11-150, 151-300., or >300 mg, the adjusted odds ratios for delivering a newborn with growth retardation were 1.00, 1.28 (95% CI 1.04-1.59), 1.42 (95% CI 1.07-1.87), and 1.57 (95% CI 1.05-2.33), respectively. Caffeine intake however, was not related to preterm delivery or low birth weight.
reproductive toxicity (low birth weight)

14-MAR-2001 (500)

Remark: reproductive toxicity (low birth weight)
The effect of alcohol and caffeine consumption on birth weight and the possible interaction of these substances with smoking was investigated in 628 women who where interviewed at their first visit to a maternity hospital. A significant reduction in birth weight was found to be associated with an average daily alcohol consumption of three drinks or more after gestational age, infant sex, maternal age, pariy, weight, and height, and ciagrette smoking hab been controlled for. The relation observed between caffeine and birth weight disappeared after adjustment for smoking.

07-MAR-2001 (501)

Remark: In a prospective study of 712 pregnancies the association between maternal smoking, alcohol, and caffeine consumption and fetal growth was examined. Patients were interviewed at entry into care (12.9 +- 4.3 weeks), and at 28 and 36 weeks of gestation. Caffeine consumption showed no relation to fetal growth, even among heavy consumers, although they were relatively few. Low birthweight is implicated by smoking at any point in pregnancy, and moderate alcohol drinking in the early months.
reproductive toxicity (low birth weight)

07-MAR-2001 (502)

Remark: A matched case-comtrol study to investigate the effects of caffeine intake during pregnancy on birth weight was conducted in 401 cases and 802 controls. Crude analyses showed no effect of caffeine on low birth weight, preterm births or intrauterine growth retardation. The results did not change after allowing for confounders.
reproductive toxicity (low birth weight)

14-MAR-2001 (503)

Remark: A prospective study of 3,891 antenatal patients at Yale-New Haven hospital was conducted (1980-1982). The effects of caffeine consumption on mean birth weight, mean gestational age, rates of low birth weight and preterm deliveries and intrauterine growth retardation were assessed. The level of caffeine consumption was divided into three categories; 1-150 mg/d, 151-300 mg/d, and >300 mg/d. A significant dose-response relationship between caffeine consumption during pregnancy and risk of having a low birth weight infant was found. Maternal caffeine intake seems to exert an effect on birth weight through growth retardation in term newborns.
reproductive toxicity (low birth weight)

14-MAR-2001 (504)

Remark: reproductive toxicity (low birth weight)
The aim of the study was to examine the association between maternal caffeine consumption and low birth weight, intrauterine growth retardation, and prematurity, adjusting for multiple confounders (interviews on 1,230 women with singleton live births). The crude odds ratio (OR) for intrauterine growth retardation in infants of women reporting heavy caffeine consumption (>300 mg/day) was 3.86 (95% CI 1.80-8.40) which decreased to 2.90 (95% CI 1.23-6.87) after controlling for confounding factors. The adjusted OR for low birth weight and heavy caffeine consumption was also increased (OR = 2.05, 95% CI 0.86-4.88). Reduction of daily caffeine intake (>300 mg to <300 mg) early in pregnancy resulted in lower risks of delivering infants with either intrauterine growth retardation or low birth weight. Preterm delivery appeared to be unrelated to caffeine intake.

07-MAR-2001 (505)

Remark: reproductive toxicity (low birth weight)

review: toxic fetal effect: IUGR (<250 g at term); reported rate of occurence: 7.5% (177/2357) vs. 4.7% (47/998) in unexposed controls; comments: heavy maternal coffee intake; incidence of IUGR increased to 9.9% (34/343) in neonates of mothers who also smoked regularly during pregnancy.

07-MAR-2001 (506)

Remark: reproductive toxicity (low birth weight)
The association of plasma caffeine concentrations during pregnancy with growth was examine. Stored plasma was available for 1,500 women who had provided a blood sample on

at least one occasion and for 640 women who had provided a sample on all three occasions (at booking for delivery, 28 weeks, and 36 weeks). Caffeine intake showed no changes during pregnancy, but blood caffeine concentration rose by 75 %. Although caffeine intake increased steadily with increasing cotinine concentration above 15 ng/ml, blood caffeine concentrations fell. Caffeine consumption was inversely related to adjusted birth weight, the estimated effect being a 1.3% fall in birth weight for a 1000 mg per week increase in intake (95 % CI 0.5-2.1). The apparent caffeine effect was confined to cigarette smokers, among whom the estimated effect was -1.6%/100 mg a week after adjustment for cotinine. Adjusted birth weight was unrelated to blood caffeine concentrations overall, after adjustment for cotinine, or among current smokers. Blood caffeine concentrations during pregnancy are not related to fetal growth, but caffeine intake is negatively associated with birth weight, with this effect being apparent only in smokers.

14-MAR-2001 (507)

Remark: reproductive toxicity (low birth weight)
The association between coffee consumption in pregnancy and fetal growth was investigated in a retrospective unmatched case-control study in 356 mother/baby pairs with intrauterine growth retardation and 356 mother/baby pairs with appropriate growth for gestational age. The proportion of mothers who delivered IUGR babies increased as the average consumption of coffe increased. The tendency for heavy coffee drinkers to deliver IUGR babies remained after controlling for alcohol intake and cigarette smoking.

07-MAR-2001 (508)

Remark: reproductive toxicity (low birth weight)
The effect of caffeine consumption during pregnancy on birth weight and its possible interaction with smoking was examine in 1,001 women who were interviewed during their first 3 days after delivery. A significant reduction in birth weight was found to be associated with an average caffeine intake of >=71 mg/day, after adjustment for gestational age, infant sex, parity, and maternal height and weight, but only in infants born to nonsmoking mothers.

07-MAR-2001 (509)

Remark: In a population-based cohort study of 7,855 livebirths

conducted in California, USA, the relation of maternal decaffeinated and caffeinated coffee consumption during pregnancy to fetal growth and gestational duration was examined (questionnaire, primarily Hispanic and Non-Hispanic white women, mean age was 25 +/- 6 years). Compared with women who drank neither decaffeinated nor caffeinated coffee, those who consumed decaffeinated coffee showed no increased odds of small-for-gestational age birth, low birth weight or preterm delivery, nor lowered mean birth weight or shortened mean gestational age. Women who consumed caffeinated coffee alone had an adjusted odds ratio of 1.3 (95% confidence interval (CI) 1.0-1.7) for preterm delivery, whereas those who consumed both caffeinated and decaffeinated coffee had an adjusted odds of 2.3 (95% CI 1.3-4.0).
reproductive toxicity (low birth weight)

07-MAR-2001 (510)

Remark: A prospective study was performed to examine the effect of alcohol and caffeine consumption on birth weight in 414 smoking mothers. When alcohol, caffeine, and smoking were analysed together, alcohol and caffeine were both associated with reduction in birthweight. Alcohol was associated with a reduction of up to 8% after adjusting for tobacco and caffeine intake, and caffeine was associated with a reduction of up to 6.5% after adjusting for tobacco and alcohol intake. Heavy smoking women (>=13 cig/day), heavy drinkers (>= 100 g/week), and high caffeine intake (>= 2801 mg/week) had a predicted reduction in mean birth weight of 18%.
reproductive toxicity (low birth weight)

14-MAR-2001 (511)

Remark: A case-control study, examing the effect of first trimester maternal caffeine consumption on low wirthweight in retrospectively followed 9,564 pregnancies. Heavy consumption (> 3 servings/day) of coffee, cola and >300 mg/day of caffeine from all sources was associated with a marignally increased risk of low birthweight.
reproductive toxicity (low birth weight)

31-AUG-2001 (512)

Remark: Effect of maternal caffeine consumption throughout pregnancy on fetal growth was studied in 2,714 women who dlivered a liveborn infant. Average caffeine intake during month 1 of pregnancy was higher than for month 7 (72.4 vs. 54.0 mg per day). Consumption of >300 mg caffeine per day during month 1 and during month 7 was not associated with intrauterine growth retardation. There was little evidence for any effect modification due to cigarette smoking on the caffeine association.
reproductive toxicity (low birth weight)

Reliability: (2) valid with restrictions
acceptable study, meets basic scientific principles
05-DEC-2001 (513)

Remark: reproductive toxicity (low birth weight)
retrospective cohort study, RR=1.59 (1.44-1.75) comparing low birth weight caffeine exposure (>150 caffeine mg/d) to controls
Reliability: (2) valid with restrictions
basic data given, restrictions
14-JAN-2002 (514)

Remark: An association between an increasing paraxanthine concentration during the third trimetser and an increasing risk of reduced fatel growth only among women who smoked. However, since paraxanthine cocnentrations could not be related to an amount of caffeine consumption the results cannot be used for an quantitative assessment.
Reliability: (2) valid with restrictions
acceptable study, meets basic scientific principles
21-OCT-2002 (515)

Remark: A study with relative good assessment of exposure and confounding factors does not support an association between moderate caffeine consumption and reduced birth weight, gestational age, or fetal growth.
Reliability: (2) valid with restrictions
acceptablle study, meets basic scientific principles
21-OCT-2002 (516)

Remark: Heavy coffee drinking (7 >= cups per day) occurs in 13 % of the study cohort, while the incidence among mothers of low birth weight infants was 21.4 %. Increasing consumption of coffee appeares to be associated with increasing rates of prematurity in all subclasses. Among heavy coffee drinkers, there is a large proportion of smokers (63.5 %) and the coffee effect on prematurity appears to be entirely explainable by the association with smoking.
reproductive toxicity (fetal loss, abortion)
14-MAR-2001 (517)

Remark: A case-control study in 331 women with fetal loss and 993 controls with normal pregnancy was done to determine the influence of caffeine intake before and during pregnancy and the risk of fetal loss. The adjusted ORs for fetal loss associated with caffeine intake before pregnancy were 1.29 (95% CI 0.85-1.95) for 48 to 162 mg; 1.37 (95% CI 0.92-2.04) for 163 to 321 mg; and 1.85 (95% CI 1.18-2.89) for more than 321 mg. The respective adjusted ORs for caffeine intake during pregnancy were 1.5 (95% CI 0.82-1.63), 1.95 (95 % CI 1.29-2.93), and 2.62 (95% CI 1.38-5.01). OR increased by a factor of 1.22 (1.10 to 1.34) for each 100 mg of caffeine ingested daily during pregnancy. The results of this study are discussed controversely by other authors.
reproductive toxicity (fetal loss, abortion)
05-MAR-2001 (518) (519) (520) (521)

Remark: Prospective information gathered through the course of pregnancy, perinatal measurements, and retrospective data collected postnatally were used to investigate the changing pattern and effects of caffeine use of 286 women. During pregnancy most women continued to consume caffeine but usually at lower intake levels. After pregnancy, caffeine consumption tended to persist at reduced levels for several months and then returned to prepregnancy patterns. Maternal caffeine intake of more than 300 mg daily during pregnancy was associated with lowered birth weight and smaller head circumference of the infant after accounting for nicotine use. No relationship was apparent between maternal caffeine use and the incidence of caesarian sections, brech births, miscarriages or premature birth.
reproductive toxicity (fetal loss, abortion)

15-FEB-2001 (522)

Remark: A case-control study in 607 cases and 1,284 controls was conducted to evaluate the potential association between caffeine consumption during the first trimester of pregnancy
an spontaneous abortion. The crude odds ratio for heavy caffeine consumption (<300 mg/day) was 1.55 (95% CI 1.04-2.31), which decreased to 1.22 (95% CI 0.8-1.87) after controllin gfor confounding factors. For these heavy users, nausea modified the association of spontaneous abortion and caffeine; heavy caffeine consumers reporting nausea had a doubled risk for spontaneous bortion (adjusted OR=2.1, 95% CI 1.2-3.7), in contrast to those who did not report nausea (adjusted OR=0.53, 95% CI 0.27-1.04).
reproductive toxicity (fetal loss, abortion)

07-MAR-2001 (523)

Remark: reproductive toxicity (fetal loss, abortion)
The effects of caffeine ingestion during pregnancy was examined in a total nuber of 9,921 healthy pregnant women with gestational age after 24 weeks. The women who drank more than 5 cups of coffee per day had a high incidence of impending abortion, premature labor, and fetuses small for gestational age. The heavy coffee drinkers (more than five cups) among the pregnant women had high rates of spontaneous
abortion, chromosomal abnormality and congenital multi-anomalies. The autors stress that the multiple socioeconomic varibales might be more important than any direct effect of caffeine.

14-MAR-2001 (524)

Remark: reproductive toxicity (fetal loss, abortion)
The association between smoking and caffeine intake during pregnancy and preterm birth was investigated in a follow-up study in 4,111 nulliparous women. The overall rate of preterm delivery was 4.3 %. Smokers had a 40 % higher risk of preterm birth compared with non-smokers. Among women with
an intake of less than 400 mg of caffeine per day no

difference in the risk of preterm birth between smokers and nonsmokers was found. However, among women with an intake of more than 400 mg of caffeine per day, the risk of preterm birth was increased almost threefold among smokers compared to nonsmokers. Furthermore, among women with high intake of caffeine a dose-response relationship was found.

05-MAR-2001 (525)

Remark: reproductive toxicity (fetal loss, abortion)
The relation between caffeine beverage consumption and spontaneous abortion in 2,967 pregant women was investigated. As compared with abstention from caffeine beverages (coffee, tea, and soda), the adjusted odds ratios for spontaneous abortion associated with consumption of 1-150, 151-300, and >300 mg caffeine daily were 0.81 (95% CI 0.54-1.20), 0.89 (95% CI 0.48-1.64), and 1.75 (95% CI 0.88-3.47), respectively. Drinking >= 3 cups of tea or coffee was associated with elevated risks of spontaneous abortion (adjusted odds ratio = 2.33, 95% CI 0.92-5.85; and adjusted odds ratio = 2.63, 95% CI 1.29-5.34).

07-MAR-2001 (526)

Remark: reproductive toxicity (fetal loss, abortion)
The association between coffee intake in pregnancy and risk of spontaneous abortion was investigated in a case-control study in 782 cases and 1,543 controls. The corresponding multivariate odds ratios of spontaneous abortion, in comparison with non-drinkers, were 1.2, 1.8, and 4.0, respectively, for drinkers of 1, 2 or 3, and 4 or more cups of coffee per day. No relationship emerged between maternal decaffeinated coffee and cola drinking in pregnancy, as well as paternal coffee consumption, and risk of spontaneous abortion. With regard to duration in years of coffee drinking, the estimated multivariate odds ratio of spontaneous abortion were, in comparison with non-coffee drinkers, 1.1 (95 % CI 1.5-2.6) for women reporting a duration of coffee consumption <=10 or >10 years.

05-DEC-2001 (527)

Remark: reproductive toxicity (fetal loss, abortion)
The relation of moderate to heavy caffeine consumption during pregnancy to spontaneous abortion and abnormal fetal growth was examined. Literatur data (case-control or cohort studies) were evaluated statistically. There was a small but statistically significant increase in the risk for spontaneous abortion and low birth weight infants in women consuming more than 150 mg/day during pregnancy. However, a possible contribution to these results of maternal age, smoking, ethanol use, or other confounders could not be excluded.

07-MAR-2001 (528)

Remark: reproductive toxicity (fetal loss, abortion)

The association between maternal caffeine consumption and the risk of spontaneous abortion was examined in a population-based prospective study. The study population comprised 575 women dilvering singleton livebirth and 75 women who had spontaneous abortions. Maternal coffee consumption before pregnancy did not increase the risk of spontaneous abortions, whereas maternal caffeine during the first trimester after nausea started might increase risk of spontaneous abortion (risk ration = 5.4, 95% CI 2.0-14.6 for caffeine consumption >= 300 mg per day compared with <20 mg per day).

14-MAR-2001 (529)

Remark: reproductive toxicity (fetal loss, abortion)
The aim of the study was to examine whether caffeine consumption during pregancy is associated with spontaneous abortion of intrauterine growth retardation. A total of 431 pregnancies was evaluated. After adjusting for other risk factors (smoking, maternal weight), no statistically significant effect of caffeine consumption on spontaneous abortion or intrauterine growth retardation was seen.

07-MAR-2001 (530)

Remark: A cohort of 431 women was monitored throughout pregnancy to determine caffeine exposure, exposure to other risk factors, fetal growth, and pregnancy outcome. The mean first trimester caffeine consumption was not significantly higher in women who aborted than in women who delivered liveborn infants. the adjusted OR for spontaneous abortion was 1.15 (95% CI 0.89-1.49). Early fetal growth was not affected by caffeine. The adjusted ORs were 1.11 (95% CI 0.88-1.40) for decreased birth weight and 1.09 (95% CI 0.86-1.37) for smaller head circumference.
reproductive toxicity (fetal loss, abortion)

14-MAR-2001 (531)

Remark: In a prospective study of 5,144 women the relation between spontaneous abortion and caffeine consumption was examined. Neither total estimated caffeine nor individual caffeinated beverage consumption during the first trimester was associated with an appreciable increase in risk for spontaneous abortion. The adjusted OR for consumption of greater than 300 mg per day of caffeine was 1.3 (95% CI 0.8-2.1). The adjusted OR for spontaneous abortion related to consumption of three or more cups of decaffeinated coffee during the first trimester was 2.4 (95% CI 1.3-4.7).
reproductive toxicity (fetal loss, abortion)

14-MAR-2001 (532)

Remark: reproductive toxicity (fetal loss, abortion)
The association of caffeine from beverages with spontaneous abortions of knwon karyotype was investigated. Spontaneous abortion (cases were classified as chromosomally normal (n=510) or chromosomally aberrant (n=389) and, within the latter category, by type of aberration (237 trisomies, 54

monosomiesX, 49 triploidies, 49 others). Controls registered for prenatal care before 22 weeks gestation and delivered at 28 weeksor later (n=1,432). Caffeine intake in the perifertilization period did not differ among case groups and controls. For the highest category, 225+ mg/day, odds ratios , adjusted forpayment group ans maternalage, were 1.0 for chromosomally normal cases, 0.9 for trisomies, 1.6 for monosmiesX, and 0.8 for triploidies. Although the proportion of subjects with intake of 225+ mg/day of caffeine was higher in cases than in controls, it was similar for those with chromosomally normal and aberrant losses (OR=1.2, 95 % CI 0.8-1.8). Caffeine intaked in the perifertilization does not influence the risk of chromosomally normal loss or trisomy. For monosomy X and triploidy, no strong associations were observed.

07-MAR-2001 (533)

Remark: A population group consisting of 800 households of women who recently had been pregnant was surveyed to determine the level of consumption of a variety of beverages. Of a subgroup of 16 women identified as having an estimated daily intake of caffeine of 600 mg or greater, 13 had experienced a reproductive loss in the form of spontaneous abortion (eight) or stillbirth(five), two had given birth to premature infants, and only one had an uncomplicated delivery. An inordinately high rate of reproductive loss also was noted in 13 households where the man´s estimated daily intake of caffeine was grater than 600 mg. The authors stated that a cause-relationship cannot be determined by this type of retrospective study.
reproductive toxicity (fetal loss, abortion)

31-AUG-2001 (534)

Remark: In a prospective cohort study, 3,135 pregnant women were followed to evaluate the association of caffeine consumption during pregnancy with late first- and second-trimester spontaneous abortion. Almost 80 % of pregnant women used some caffeine; among useres the average daily intake was 99.3 mg from all sources. The adjusted relative risk of miscarriage after caffeine consumption >= 151 mg daily was 1.73 (p=0.03). Light caffeine use (1 to 150 mg daily) was associated with increased risk of spontaneous abortion only among women who aborted in their pregnancy (RR=4.18, p=0.04).
reproductive toxicity (fetal loss, abortion)

16-MAR-2001 (535)

Remark: A population-based, case-control study of early spontaneous abortion was performed in 562 women who had spontaneous abortion at 6 to 12 completed weeks of gestation and 953 women who did not have spontaneous abortion and were matched to the case patients. Among nonsmokers, more spontaneous abortion occurred in women who ingested at least 100 mg caffeine per day than in women who ingested less than 100 mg per day, with the increase in risk related

to the amount ingested (100 to 299 mg per day: odds ratio 1.3, 95 % CI 0.9 to 1.8; 300 to 499 mg per day: odds ratio 1.4, 95 % CI 0.9 to 2.0; and 500 mg and more per day: odds ratio 2.2, 95 % CI 1.3 to 3.8). Among smokers, caffeine ingestion was not associated with an excess risk of spontaneous abortion.
reproductive toxicity (fetal loss, abortion)

Reliability: (2) valid with restrictions
acceptable study, meets basic scientific principles

05-DEC-2001 (536)

Remark: In a nested case-control study, serum paraxanthine was measured in 591 women who had spontaneous abortions at less than 140 days´ gestation and in 2558 matched women . A total of 487 women who had spontaneous abortions and 2087 controls had quantifiable serum paraxanthine concentrations. The odds ratio for spontaneous abortion was not significantly elevated in the women who had serum paraxanthine concentrations of 1845 ng/ml or lower. The adjusted odds ratio for spontaneous abortion among women with serum paraxanthine concentrations higher than 1845 ng/ml, as compared with women who had concentrations below 50 ng/ml, was 1.9, 95 % CI 1.2 to 2.8.
reproductive toxicity (fetal loss, abortion)

Reliability: (2) valid with restrictions
acceptable study meets basic scientific principles

05-DEC-2001 (537)

Remark: Nausea in pregnancy effetcs the exposure to caffeine. Intake is often reduced in early pregnancy. Although this this reduction is partly an epiphenonmenon in its own right, it is more marked in the presence of nausea. Nausea is affected by the outcome. It manifests with differing frequencies according to whether a pregnancy will terminate either as a miscarriage or as a live birth. Nausea indicates a concurrently surviving pregancy.
reproductive toxicity (fetal loss, abortion, review)

Reliability: (4) not assignable
review

05-DEC-2001 (538)

Remark: reproductive toxicity (fetal loss, abortion)
Retrospective cohort study, RR 1.23 (1.18-1.29) comparing spontaneous abortion in caffein exposure (>150 caffeine mg/d) to controls.

Reliability: (2) valid with restrictions
basic data given, restrictions

14-JAN-2002 (539)

Remark: reproductive toxicity (fetal loss, abortion)
retrospective cohort study, RR 2.89 (1.92-4.35) comparing spontaneous abortions in caffeine exposure (>150 caffeine mg/d) to controls

Reliability: (2) valid with restrictions
basic data given, restrictions

14-JAN-2002 (540)

Remark: In a retrospective study the drug consumption during pregnancy with congenital abnormalities in infants was examined in 1,369 mothers. In mothers taking caffeine no increased numbers of congenital abnormalities in infants were observed.
reproductive toxicity (birth defects)
19-FEB-2001 (541)

Remark: In a case-control study of 2,030 malformed infants, six selected birth defects were evaluated in relation to maternal ingestion of caffeine intake during pregnancy. 380 infants with inguinal hernia, 299 with cleft lip, 277 with cardiac defetcs, 194 with pyloric stenosis, 120 with isolated cleft palate, and 101 with neural tube fusion defects were compared to 712 other malformed infants who served as control. None of the point estimates of relative risk was significantly greater than unity.
reproductive toxicity (birth defects)

13-MAR-2001 (542)

Remark: 755 pairs of mothers of malformed children and their controls were studied to examine an association between coffee consumption and malformations. The coffee consumption during pregnancy was similar for the mothers of malformed or non-malformed children. The comparison of the mothers drinking at least four cups of coffee a day during pregnancy with those not consuming coffee at all showed a RR of 1.0 (95% CI 0.7-1.3).
reproductive toxicity (birth defects)

13-FEB-2001 (543)

Remark: reproductive toxicity (birth defects)
Retrospective information on maternal caffeine intake during pregnancy and abnormal offspring was obtained by questionnaire during 1989. 14 cases were examined. Spontaneous abortion or stillbirth was associated with high level of caffeine consumption (about 1,000 mg) each day. Low birth weight infants or premature birth infants were caused by caffeine intake >200 mg a day. Developmental delay or central nervous system dysfunction was also associated with caffeine intake >200 mg a day. Congenital anomalies were noted also with >200 mg caffeine per day.

27-FEB-2001 (544)

Remark: Interviews and medical-record data of 12,205 were analysed to evaluate the relationshipbetween coffe consumption and adverse outcomes of pregnancy. After controlling for smoking, other habits, demographic characteristics, and medical history no relation between low birth weight or short gestation and heavy coffee consumption was found. Furthermore there was no excess of malformations among coffee drinkers.
reproductive toxicity (birth defects)

13-MAR-2001 (545)

Remark: A large North American study followed 5378 women exposed during pregnancy to caffeine-containing drugs for possible malformations in their offspring. For all malformations considered together (n=350) the RR was 0.98. For malformations at individial sites, the RRs ranged from 0.70 to 1.2 (nonsignificant).
reproductive toxicity (birth defects)

20-AUG-2001 (546)

Remark: reproductive toxicity (fetal effects)
The effect of caffeine on fetal heart rate pattern was evaluated. A 3-fold prolongation of metabolism and duration of action of caffeine is observed in pregnant women. Sensitivity of the fetal heart to caffeine appears as early as in the first trimester of prenatal life. Caffeine produces age- and concentration-dependent positive chrono- and inotropic effects.
27-FEB-2001 (547)

Remark: reproductive toxicity (fetal effects)
The acute maternal and fetal cardiovascular effects of caffeine were studied. Cafffein citrate was administered to 7 caffeine-naive gravidas longitudinally at 25.7 (+/-0.7) and 36.1 (+/-0.7) weeks' gestation. Significant before and after caffeine differences, regardless of gestational age, were noted for maternal pulse (decreased), diastolic blood pressure (increased), mean arterial blood pressure (increased), uterine artery systolic-to-diastolic (S/D) ratio (increased), fetal heart rate (decreased), fetal heart rate accelerations (increased), and fetal aortic peak velocities (increased). According to the authors, these results suggested that ingestion of moderate amounts of caffeine citrate to caffeine-naive gravidas significantly affected both the fetal and maternal cardiovascular system.
27-FEB-2001 (548)

Remark: A longitudinal cohort study of 20 normal third-trimester pregnancies was performed to observe whether the level of long-term maternal caffeine ingestion influenced intrauterine fetal behavior. Fetuses of mothers whose mean daily caffeine intake did not exceed 200 mg exhibited temporal distribution of fetal behavioral states that resemble those found in most normal third-trimester pregnancies.
reproductive toxicity (fetal effects)
05-MAR-2001 (549)

Remark: Newborn cardiac arrhythmias associated with maternal caffeine
use during pregnancy were investigated. Daily maternal caffeine intake was >500 mg/day in the so called "caffeine group" (16 persons) and <250 mg/day in the so called "control group" (56 subjects). Urine screen of all infants of the women consuming >500 mg/day was positive for caffeine. Tachyarrythmia, premature atrial contractions, fine tremors, and tachypnea were greater in the caffeine group than in the control group.
reproductive toxicity (effects in infants)
05-MAR-2001 (550) (551)

Remark: Maternal caffeine consumption was associated with an increased risk of central and obstructive apneas in the infant. The meachnism for this effect is not clear; however, it may be related to an increased number of adenosine receptors in the brain stem.
reproductive toxicity (effects in infants, review)

28-MAR-2001 (552)

Remark: In a case-control study surveying parents of 393 sudden infant deaath syndrome victims the association to maternal caffeine consumption during pregnancy was examined. Infants whose mothers had heavy caffeine consumption (400 mg/day or more) throughout their pregnancy had a significantly increased risk for SIDS (OR 1.65, 95 % CI 1.15-2.35).
reproductive toxicity (effects in infants)

05-MAR-2001 (553)

Remark: Linear and threshold effects of prenatal caffeine on pregnancy outcome and offspring development were examined in a cohort of appr. 500 offspring. Prenatal caffeine exposure was not related to most newborn and infant outcome measures, including height, weight or head circumference, or to individually administered IQ and attention tests at 7 years of age. Only one isolated dependent variable of the many was siginificantly associated with prenatal caffeine exposure: breech presentation.
reproductive toxicity (effects in infants)

14-MAR-2001 (554)

Remark: reproductive toxicity (effects on sperms)
The potential contribution of common lifestyle exposures (smoking, caffeine, and alcohol) to the aneuploidy load in human sperm was investigated in a cross-sectional, observation study. Sperm specimen were observed from 45 healthy men 19-35 years of age. Sperm FISH (fluorescence in situ hybridization) was used to determine aneuploidy and diploidy frequencies for chromosomes X, Y, and 18. Caffeine was significantly associated with increased frequencies of sperm aneuploidy XX18 and XY18, doploidy XY1-18 and the duplication phenotype YY18-18 controlling for alcohol, smoking and donor age.

13-FEB-2001 (555)

Remark: reproductive toxicity (effects on sperms)
The aim of the study was to determine whether sperm nuclear size, shape, and chromatin texture parameters are associated with lifestyle exposures including smoking, caffeine and alcohol consumption. Eighty-six healthy male volunteers, aged 18-35 years, provided a semen, blood, and urine sample and completed a questionnaire. No significant effect on sperm morphometric parameters was found.

14-MAR-2001 (556)

Remark: review (general)

27-AUG-2001 (557)

5.11 Additional Remarks

Type: Behaviour

Remark: The aim of the study was to evaluate behavioral effects of exposure to the test substance (via the drinking water)

during gestation and/or lactation. Dams were exposed to 26 or 45 mg/kg during gestation or to 25 or 35 mg/kg during lactation or to the two low or high doses during both gestation and actation. Open-field behavior and latencies of emerge from a darkened chamber of the offspring was recorded at 1, 2, 4, and 6 months after birth. Behavioral impairments were recorded at 1 to 6 months after birth in male and female rats and included less locomotor and rearing activity, reduced tendecies to emerge and increased defacation in the open field.

Test substance: caffeine

30-JAN-2002 (558)

Type: Biochemical or cellular interactions

Remark: Repeated oral administration of the test substance (100, 200, 400 and 800 ug/ml in the drinking water for eight weeks or application by gavage of 40 and 160 mg/kg for four days) to male Swiss mice increased the biochemical activity in liver and lung cells as it was demonstrated by enhancement of AHH, Cytochrome P-450, GST and GSH activity.

Test substance: caffeine

22-AUG-2000 (559)

Type: Biochemical or cellular interactions

Remark: The effect of the test substance on acetaminophen-induced hepatotoxicity was studied in adult male Sprague-Dawley rats (uninduced and induced). Hepatic glutathione (GSH) was determined 4 h after dosing. No hepatotoxicity was observed after administration of the test substance alone (200 mg/kg). Depleted GSH was noted; however, according to the authors, this was most likely caused by decreased core body temperature. In phenobarbital-induced rats, the test substance substantially potentiated the hepatotoxicity of acetaminophen. No potentiation was seen in rats induced with 3-methylcholanthren. According to the authors, the most likely mechanism for the effects observed was activation of the phenobarbital-inducible forms of cytochrom P-450 toward formation of acetaminophen reactive metabolites by caffeine.

Test substance: caffeine

31-AUG-2000 (560)

Type: Biochemical or cellular interactions

Remark: Contraction of canine cerebral artery induced by the test substance was studied in cultures of basiliar cerebral arterial rings. In the complete absence of Ca2+, the test substance (10 mM, ca. 1942 ug/ml) induced transient contractions followed by relaxation in K+-depolarized cerebral vascular tissue.

Test substance: caffeine

24-AUG-2000 (561)

Type: Biochemical or cellular interactions

Remark: The effect of the test substance on gap junctional communication in V79 Chinese hamster lung fibroblast cells was studied using the V79/metabolic cooperation assay (vehicle: media). No substance-related effects were seen at concentrations or up to 500 ug/ml.

Test substance: caffeine

31-AUG-2000 (562)

Type: Biochemical or cellular interactions

Remark: The caffeine-induced uncoupling of mitosis from the completions of DNA replication was studied in Syrian hamster fibroblasts (BHK cells). The cells were incubated for 24 h, then treated with medium, calf serum and hydroxyurea for another 14 h, and finally given the test substance along with colcemid. The test substance induced the translation or stabilized the protein products of mitosis-related RNA that accumulated in S-phase cells when DNA replication was suppressed.

Test substance: caffeine

31-AUG-2000 (563)

Type: Biochemical or cellular interactions

Remark: The effect of the test substance on the contact feeding phenomenon in Chinese hamster V79 cells, 6-TG-resistent clone and T2-14 cells was investigated. The test substance did not give any increase of the recovery in the contact-feeding assay. According to the authors, this result suggested that the test substance did not inhibit the phenomenon of metabolic cooperation.

Test substance: caffeine

31-AUG-2000 (564)

Type: Biochemical or cellular interactions

Remark: The effect of the test substance on the disposition of brain serotonin was studied. Male young Wistar rats were given caffeine containing beverages or fed diets containing caffeine from various sources of caffeine plus adenosine for 1 or 4 days. Brains were collected for fluorimetric assay of tryptophan, serotonin and 5HIAA. Serum cAMP concentations were determined by radioimmunoassay. Brain tryptophan, serotonin and 5HIAA and serum cAMP were significantly increased. Adenosine partially reduced the caffeine-induced increase in brain serotonin but increased cAMP levels. Brain findings were similar after 1 and 4 days.

Test substance: caffeine

31-AUG-2000 (565)

Type: Biochemical or cellular interactions

Remark: The effect of the test substance on urinary electrolyts and renal prostaglandin (PG) synthesis was studied. Female Sprague-Dawley rats were given a single dose of the test substance (1.5, 5, 15, 50 mg/kg). No effect was seen at 1.5 mg/kg. Renal function was altered at 5 mg/kg and above. At 50 mg/kg, increased excretion of Na+ and Ca2+ was noted; at later time, K+ and Ca2+ decreased below control. Increased PGE2 and 6-keto-PGF1-alpha excretion was observed.

Test substance: caffeine

31-AUG-2000 (566)

Type: Chemobiokinetics general studies

Remark: Male rats were given 1, 2.5, 10 and 25 mg/kg of the test substance i.v. and the kinetics found were compared with liver perfusion patterns. For doses less than 10 mg/kg or mg/l, caffeine blood or perfusate concentrations/time profiles followed first order kinetics and the elimination rate constant (average 0.013/min) and half-life (55 min) were similar for in vivo and ex vivo conditions. After doses of 10 and 25 mg/kg or mg/l, kinetics were nonlinear. The area under the blood or medium concentration-time curve increased; however, this increase was not dose-related.

Test substance: caffeine

31-AUG-2000 (567)

Type: Chemobiokinetics general studies

Remark: Absorption, distribution, metabolism and excretion in animals was summarized:
Caffeine absorption and distribution from gastrointestinal tract is rapid and complete and it is distributed to all body fluids and appeared in all tissues within 5 min. There is no accumulation of caffeine or its metabolites in any organ even after high doses. No blood-brain barrier or placental barrier was detected. The fraction bound to plasma albumin varies from 10 to 30%. It is eliminated by various species by first-order kinetics, described by a one-compartment open model system. The half-life for several species ranged between 0.7 to 12 h (rats to baboons) and a mean volume of distribution of 0.8 l/kg has been reported for various species. Decreased as well as increased half-lifes were found in pregnant animals. Caffeine is metabolized by liver microsomal mixed-function oxidases and can increase metabolizing enzymes at high doses (75 mg/kg). Caffeine is eliminated in animals by biotransformation to dimethylxanthines, dimethyl- and monomethyluric acids and uracil derivatives. Differences in formation and elimination of metabolites were noted in rats, mice and Chinese hamsters and mainly in monkeys, where it is almost completely metabolized to theophylline. In contrast, the acetylated uracil derivative,

5-acetylamino-6-formylamino-3-methyluracil, one of the most important metabolites in human, was not found in rodents or other species.
Pharmacokinetic differences were recognized in mice after oral administration, which may account for interstrain variation in toxicity and in rabbits two subpopulations were described with slow or rapid metabolizing capacity (IARC, 1991).
For further reviews see Nau,1987; Arnaud,1993; Arnaud et al.,1988; Sawynok and Yaksh, 1993).

Test substance: caffeine

Reliability: (4) not assignable
review, comparable with relaibility 2, data from Handbook or collection of data, selected for ICCA RSS

Flag: Critical study for SIDS endpoint

30-JAN-2002 (568) (569) (72) (570) (571)

Type: Chemobiokinetics general studies

Remark: The disposition of the test substance and its dimethylxantine metabolites (theobromine, theophylline and paraxanthine) was studied in non-pregnant and 20-day pregnant rats. The rats were administered a single oral dose of the test substance (5 or 25 mg/kg). Peak plasma levels were reached at 1-3 hours in all fluids and tissues examined. However, the elimination phase differed significantly between pregnant and non-pregnant rats. At the high dose level, plasma half life was significantly lower in the pregnant rats; at the low dose level, elimination half life was similar in both groups. Area-under-curve (AUC) values were used to compare caffeine and metabolite exposure in fetal tissue. At 25 mg/kg, peak concentrations for amniotic fluid, fetal blood, liver and kidneys were not significantly different from one another. At 25 mg/kg, peak levels in fetal liver and kidney were significantly less than those of fetal blood, amniotic blood or placenta. According to the authors, this observed increase in maternal elimination half life at the high dose level suggested that a cautionary note was sounded about caffeine intake during pregnancy.

Test substance: caffeine

21-AUG-2000 (572)

Type: Cytotoxicity

Remark: The cytotoxicity was determined in rat hepatocytes, McCoy and MDBK cells; the respective CT50 values were determined. The CT50 is the minimum test concentration inducing morphological changes or 50% cell deaths and/or 50-100% increase in LDH release and represent the mean value for all three effects.
CT50 = 1.596 mM (ca. 0.3 mg/ml) (rat hepatocytes)
CT50 = 15.44 mM (ca. 2.3 mg/ml) (McCoy cells)
CT50 = 15.87 mM (ca. 3.1 mg/ml) (MDBK cells)

Test substance: caffeine

22-AUG-2000 (573)

Type: Cytotoxicity

Remark: The acute in vitro cytotoxicity was assayed biochemically inhuman lymphocytes and resulted in LC50 values of 1020 ug/ml (LDH assay), 1200 mg/ml (DNA assay) and 800 ug/ml (MTT assay). The IC50 value for HeLa cells was 1300 ug/ml.

Test substance: caffeine; according to the authors, purity was of the highest grade commercially available

31-AUG-2000 (574)

Type: Cytotoxicity

Remark: Cytotoxicity was determined in human foreskin fibroblast cell line (HFF), human hepatoma cell line (HepG2), human melanoma cell line (Mel/27), human epidermal keratinocytes (NHEK) and in human endothelial cells (ENDO) using the Neutral Red assay. The following midpoint cytotoxicity values (NR50%) were determined:
ENDO: 5 mM (ca. 971 ug/ml)

NHEK: 18 mM (ca. 3495 ug/ml)
HEF: 19 mM (ca. 3690 ug/ml)
Mel/27: 12 mM (ca. 2330 ug/ml)
HepTG2: 15 mM (ca. 2913 ug/ml)

Test substance: caffeine

22-AUG-2000 (575)

Type: Cytotoxicity

Remark: The hepatoxicity of the test substance was studied in vitro. Isolated rat hepatocytes were incubated with the test substance at concentrations of 0, 2.5, 5.0, and 10 mM (ca. 0, 485, 971, 1942 ug/l) at 37 degree C for 60, 120, and 180 minutes. A significant, dose-and time-related loss of cell viability, as measured by cell count and lactate dehydrogenase leakage to the medium was observed.

Test substance: caffeine

31-AUG-2000 (576)

Type: Distribution

Remark: Pregnant FDA-strain Osborne-Mendel rats were administered the 14C-labelled test substance on days 12 to 15 of gestation. The test substance was applied at a dose level of 80 mg/kg/d either by gavage or via the drinking water. After administration in the drinking water, radioactivity in the blood was variable. The highest level on day 12 was 0.2%/ml blood; the highest level observed during a 24-hour sampling period averaged 5.7 ug/ml. After gavage dosing, blood radioactivity peaked of 0.4% of the dose per ml blood and declined rapidly thereafter. The highest amount observed in blood averaged 63.1 ug/ml at 1 h after dosing. The overall blood elimination half-life of radioactivity was 2.6 h in gavage-treated rats; the caffeine half-life in blood was 1.7 h. The levels of radioactivity in the fetus and maternal muscle were comparable after each method. Increased resorptions were seen in both treated groups ectrodactyly was evident in offsprings of the gavage-treated rats.

Test substance: caffeine

31-AUG-2000 (577)

Type: Excretion

Remark: After i.v. injection of 200 ug (10 uCi) to female pigs, about 68% and 17% of the radioactivity was excreted in the urine and the feces, respectively. Total excretion was ca. 85%. Topical application of 200 ug (10 uCi) resulted in a total excretion (urine and feces) of 11.8% (urinary excretion: 8.5%)

Test substance: caffeine

30-JAN-2002 (578)

Type: Immunotoxicity

Remark: The methylxanthine-induced inhibition of the antigen- and superantigen-specific activation was studied in T and B lymphocytes. The test substance (in vitro) induced the inhibition of the antigen and superantigen-specific activation of T and B lymphocytes as tested by the responses of mouse and human lymphocytes to stimulation with polyclonal T- and B-cell mitogens, antigens, and the microbial superantigen, staphylococcal enterotoxin B.
Test substance: caffeine

22-AUG-2000 (579)

Type: Immunotoxicity

Remark: Administration of the test substance (2, 6 and 18 mg/kg) for at least 120 consecutive days by gavage to male Sprague Dawley rats led to no plausible alteration of the tested immunological cell activities except an increased response to the T-cell mitogen PHA at 18 mg/kg. However, in vitro application decreased B- and T-lymphocyte proliferation; NK cell activity was not effected (neither in vivo nor in vitro).
Test substance: caffeine

22-AUG-2000 (580)

Type: Metabolism

Remark: In both humans and rats, excretion of caffeine mainly occures via urine (about 90 % dose in rats; > 95 % in humans).
Caffeine metabolism is qualitavely relatively similar in animals and humans. The main metabolic pathways are: demethylation and hydroxylation of the 8-position leading to the formation of the respective uracil and uric acid derivatives. There are, however, some quantitative differences in the metabolic profile. Humans are characterized by the importance of 3-methyl demethylation leading to the formation of paraxanthine and especially metabolites thereof through subsequent metabolic steps. The main urinary metabolites in humans are 1-methyluric acid, 1-methylxanthine, and 1,7-dimethyluric acid. In rats and mice, the metabolism of caffeine is predominantly via theobromine and theophylline. The main urinary metabolites are1,3-dimethyluracil, paraxanthine, trimethyluric acid, theophylline, and theobromine.
Caffeine metabolism decreases during pregnancy, resulting in higher serum concentrations.
Test substance: caffeine
Reliability: (2) valid with restrictions
data from Handbook or collection of data
Flag: Critical study for SIDS endpoint

30-JAN-2002 (581)

Type: Toxicokinetics

Remark: Pharmacokinetics were examined in horses after 2.5 mg/kg i.v., i.m. or p.o. application. Pharmacokinetics after i.v. were decribed by assumption of a two-compartment model and those after i.m or p.o. by assumption of one-compartment model. Half-lifes were 15.5; 18.6 and 16.4 h after i.v., i.m. of p.o. application, respectively. Pharmacokinetic parameters differed not significantly among the administration routes.

Test substance: caffeine

31-AUG-2000 (582)

Type: other

Remark: Evaluation of the genotoxicity of caffeine by the carcinogen prediction and battery section (CPSB) method on the basis of four mutagenicity assays predict that caffeine has potential for genotoxic carcinogenicity (Rosenkranz and Ennever, 1987) but the available animal bioassays clearly indicates that caffeine does not have carcinogenic potential (Grice, 1987).

Test substance: caffeine

30-JAN-2002 (583) (584) (585)

Type: other

Remark: The aim of the study was to investigate the lasting effects of early exposure to the test substance. Pregnant rats were fed the test substance (20 mg/kg/d) starting on day 9 of gestation until day 93 post partum (weaning of the pups: day 22 post partum). Thereafter the dams received caffeine-free diet and were sacrificed at day 388. In the offspring, lasting effects on the behavior (increased locomotive activity) and biochemically altered brain regions were noted.

Test substance: caffeine

31-AUG-2000 (586)

Type: other

Remark: Administration of 60 mg/kg to male BALB/c mice via the drinking water used for impregnation and gestant modified the passive avoidance behavior of offsprings. The author assessed this as preliminary indication that functional effects of fetal caffeine exposure can be expressed in a second generation.

Test substance: caffeine

22-AUG-2000 (587)

Type: other: DNA damage

Remark: The effects of the test substance on gamma-radiation induced DNA damage was studied in ataxia telangiectasia lymphoblastoid cells obtained from adult humans. The test substance potentiated the induction of chromosomal breaks in G2 arrested AT heterozygote and normal lymphoblastoid cells, but not in homozygous AT lymphoblastoid cells.
Test substance: caffeine

31-AUG-2000 (588)

Type: other: DNA damage

Remark: The DNA modifying activity of the test substance was evaluated using normal and DNA-polymerase-deficient strains of Escherichia coli. The test substance gave positive results.
Test substance: caffeine

24-AUG-2000 (589)

Type: other: anticancer effect

Remark: The inhibitory effect of the test substance on the induction of cutaneous tumors by ultraviolet rays was studied in female SPF-derived Swiss mice. A solution of the test substance (0.2% in acetone) was painted onto the ears of the mice prior to irradiation for 90 minutes. Untreated mice were used as control. According to the authors, the test substance significantly reduced the incidence of cutaneous tumors produced by UV rays (by ca. one half). No substance-related lesions were seen in nonirradiated, caffeine treated mice.
Test substance: caffeine

31-AUG-2000 (590)

Type: other: carcinogenicity in vitro

Remark: A rapid in vitro assay for carcinogencity was validated. Rauscher leukemia virus-infected rat embryo cells (2FR450 cells) were seeded into plastic flasks and incubated for 24 hours. The test substance was added to the cells (440 ug per 5.2 x 10E4 cells); control cultures received the solvent. After 72 hours of incubation at 37 degree C, cells were removed from the flasks by trypsinization and washed, after which viable cell counts were obtained. Viable cells were then seeded into dishes having a solid bottom layer of agar. The dishes were incubated at 37 degree C with a control set of dishes seeded with untreated cells (negative control) and with 3-methylcholantrene-treated cells (positive control). Three and six days later, cells were harvested and viable cells were counted. According to the authors, in cultures treated with the test substance, percent increase over control was greater than 118%. This result was judged as positive.
Test substance: caffeine

31-AUG-2000 (591)

Type: other: classification

Remark: There is inadequate evidence for the carcinogenicity of caffeine in humans and in experimental animals. Caffeine is not classifiable as to its carcinogencity to humans (group 3).

31-AUG-2000 (72)

Type: other: effect on sperm

Remark: The effect of the test substance on macaque sperm motility and interaction with the zona pellucida was studied in vitro. Semen from 6 cynomolgus macaques was incubated for 2.5 hours with the test substance at a concentration of 2 mM (ca. 288 ug/ml). Immature oocytes were placed into drops of sperm suspensions, coincubated with sperm for 30 seconds, and either fixed immediately or removed to sperm-free media and incubated 1 hour before fixation. There were no differences between treated and control cultures in the percentage of live, acrosome-reacted sperm in suspension. Treatment with the test substance significantly increased the number of sperm bound to the zona pellucida.

Test substance: caffeine

21-AUG-2000 (592)

Type: other: effect on sperm (human)

Remark: Incubation of human spermatozoa with 6 mM caffeine resulted in alteration of motility and velocity and affected the metabolism of the spermatozoa.

Test substance: caffeine

31-AUG-2000 (593)

Type: other: effect on sperm (human)

Remark: The effect of lifestyle (smoking, caffeine intake and alcohol consumption) on human sperm was studied. Samples of semen, blood and urine were collected from 86 volunteers, combined with a questionaire on demography and lifestyle. Sperm nuclear size, shape and chromatin texture parameters were measured by a computer image analysis. Results indicated no associations between the sperm nuclear morphometric parameters andage, smoking, or alcohol consumption. A weak evidence for an association with caffeine intake was seen.

Test substance: caffeine

21-AUG-2000 (594)

Type: other: gastric irritation

Remark: The aim of the study was to investigate gastric irritation and bleeding after drug administration. Grousp of 4-6 rats received a single dose of the test substance in distilled water (20 ug/ml) after a 24-hour fast. Sacrifice was 1 h after dosing. No bleeding or ulceration of the stomach was noted.

Test substance: caffeine

31-AUG-2000 (595)

Type: other: inhibition of DNA synthesis

Remark: Inhibition of DNA synthesis in mouse L5178Y cells, LS929 mouse fibroblasts and V79 Chinese hamster cells was recorded. Reduction of newly synthesized DNA was inhibited in both unradiated and ultraviolet radiated cells.

Test substance: caffeine

22-AUG-2000 (596)

Type: other: inhibiton of DNA synthesis

Remark: The HeLa DNA-synthesis inhibiton test, a rapid screen for mutagenic carcinogens was validated. HeLa cells were incubated with the test substance in the presence and absence of S-9 for 60 and 30 minutes, respectively. No mutagenic effect was observed.

Test substance: caffeine

31-AUG-2000 (597)

Type: other: maternal-fetal effect

Result: The aim of the study was to investigate the relationship between fetal exposure and cardiovascular functional effects. The test substance (100 mg/kg) was administered i.v. to pregnant Sprague-Dawley rats on day 21 of gestation. The transplacental transport of the test substance was evaluated. by obtaining maternal and fetal blood sampes (umbilical vein) at designated times after administration. Concurrent maternal-fetal electrocardiograms (ECGs) were measured and evaluated for substance-related changes. Maternal and fetal plasma caffeine levels as well as area under curve (AUC) values were proportionally related throughout the study, indicative of equal exposure to the test substance. The fetal ECG exhibited more extensive changes associated with the test substance than did the dams'. The fetal effects were not detected within the first 30 minutes, suggesting a lag period for the activity of the test substance to the fetal heart.

Test substance: caffeine

22-AUG-2000 (598)

Type: other: prevention of malformation

Remark: The prevention of limb malformations induced by the test substance by maternal adrenalectomy was studied in AKR mice. Pregnant dams were adrenalectomized on day 6 of gestation and were administered the test substance on day 11 and 12 of gestation (175 mg/kg i.p.). Control mice were administered the test substance without adrenalectomy. Fetuses were evaluated on day 18 of gestation. Thirty percent of the surving pups of contol dams were malformed compared to 7% malformed pups in the group of adrenalecomized dams. According to the authors, caffeine teratogenesis was

initiated by release of catecholamine from apparently the maternal adrenal gland.

Test substance: caffeine

31-AUG-2000 (599)

Type: other: recombinagenicity

Remark: Concentrations of 50 mM (ca. 9.7 mg/ml) or higher inhibited cell replication and induced gene segregation in Candida albicans cultured on defined complete medium. Caffeine concentrations above 150 mM (ca. 29.1 mg/ml) caused cellular inactivation. Consequently, the test substance was recombinagenic but not mutagenic for Candida albicans.
Test substance: caffeine

31-AUG-2000 (600)

Type: other: reproductive effects in vitro

Result: CD-1 mouse oocytes were exposed to the test substance at concentrations of 1, 2.5, 5, or 10 mM (ca. 194, 485, 971, 1942 ug/ml) for 10, 30, or 60 minutes (control: exposure to 10% ethanol and unstimulated aging oocytes). Pronuclear embryos from CD-1, CF-1 and B6C3F1 hybrid mice were cultured in 0.16, 0.33, 0.66, 1.25, 2.5, 5 or 10 mM (ca. 31, 64, 128, 243, 485, 971 or 1942 ug/ml) and development was scored over 96 hours of culture.
Exposure to the test substance artificially activated mouse oocytes in a concentration- and exposure time-dependent manner. The level of activation was significantly greater than that associated with aging but less than ethanol-induced activation. Caffeine-activated oocytes had limited developmental capacity compared with the ethanol-activated oocytes. The test substance affected embryo development in a dose-dependent manner with developmental inhibition and embryotoxicity.
Test substance: caffeine

31-AUG-2000 (601)

Type: other: reproductive toxicity

Remark: The embryotoxic risk of exposure to the test substance during the preimplantation period was studied in mice. Pregnant NMRI mice were given the test substance by gavage at dose levels of 24, 48, 100 and 200 mg/kg before implantation; the test substance was given in 4 divided doses. No embryotoxicity was observed at doese of up to 100 mg/kg. In mice administered 200 mg/kg, decreased fetal body weight, significantly increased percentage of retards or resorbed fetuses, and embryolethality was recorded.
Test substance: caffeine

31-AUG-2000 (602)

Type: other: review (general)

31-AUG-2000 (72) (603) (604) (605) (606) (607)

Type: other: review (mutagenicity)

Remark: Literature reviews of papers on general or selective mutagenicity and/or carcinogenicity studies

21-AUG-2000 (117) (608) (609) (610) (195) (611) (612) (613) (614) (615)

Type: other: review (mutagenicity)

Remark: Literature reviews of papers on general or selective mutagenicity and/or carcinogenicity studies

22-AUG-2000 (616) (72) (617) (618) (619) (620) (584) (621) (622)

Type: other: review (mutagenicity)

22-AUG-2000 (623) (448)

Type: other: review (reproduction)

Remark: Review about reproductive effects of caffeine

31-AUG-2000 (624) (625) (626)

Type: other: strain A mouse carcinogencity screen

Remark: Male strain A mice received i.p. doses of 8, 20 and 40 mg/kg three times a week for eight weeks and were examined 24 weeks after the first injection in a screening assay based on the accelerated induction of lung tumors. All three doses decreased the incidence of lung tumors.

Test substance: caffeine

31-AUG-2000 (627)

Type: other: teratogenicity

Remark: Caffeine induced dose-dependent malformations in a new Drosophila bioassay that was developed to screen possible malformation-inducing chemicals (exposure of developing Drosophila from egg through three larval stages by incorporating the test substance into the culture medium).

Test substance: caffeine

24-AUG-2000 (628)

Type: other: teratogenicity

Remark: The patterns of response of intact Drosophila to known teratogens were studied. Wild-type Oregon-R fly larvae were exposed to the test substance in medium over their entire morphogenic cycle (concentrations: 0.5, 1, 2, 3, 4, 5 ug/ml). Each adult fly was systematically examined for external morphological abnormalities. Substance-related effects were seen at each dose level.

Test substance: caffeine

31-AUG-2000 (629)

Type: other: teratogenicity

Remark: Forelimb buds of day 14 rat fetuses were cut into pieces and transplanted subcutaneously into athymic (nude) mice. On the 7th, 9th, and 11th day after grafting, the nude mice were treated orally with the test substance at doses of 200, 400, and 800 mg/kg. On the 20th day, the grafted tissue was examined macroscopically and histologically. The differentiation of the graft was significantly inhibited at all dose levels.

Test substance: caffeine

31-AUG-2000 (630)

Type: other: teratogenicity in vitro

Remark: The teratogenic activity of the test substance was tested in the Frog Embryo Teratogenesis Assay - Xenopus (FETAX), a teratogenicity screening test. Frog larvae were exposed to the test substance using a static renewal procedure, exposure time was 120 hours.
LC50 = 0.19 (0.18-0.21) mg/ml
LC50 = 0.13 (0.12-0.13) mg/ml (malformation)
LOEC = 0.08 mg/ml (MCIG = mean minimum concentration to inhibit growth)
TI = 1.46 (teratogenic index = LC50/EC50)

Test substance: caffeine

31-AUG-2000 (631)

Type: other: teratogenicity in vitro

Remark: In the in vitro teratogenicity screening assay using the whole chick embryo culture, the IC50 was ca. 0.525 +/- 1.6 mmol/l (ca. 102 ug/ml); IC50 = concentration that induced malformations in 50% of the embryos.

Test substance: caffeine

24-AUG-2000 (632)

Type: other: teratogenicity in vitro

Remark: The effects of the test substance on cultured whole rat embryos obtained from nulliparous Sprague-Dawley rats was studied. Exposure to 1 mmol/1 ml serum (ca. 0.2 ug/ml) on cultured whole rat embryos delivered on gestation day 10 and cultured to gestational day 12 in vitro resulted in a multiple delay in development.

Test substance: caffeine

31-AUG-2000 (633)

Type: other: teratogenicity in vitro

Remark: The developmental toxicity of the test substance was studied in frog larvae. In vitro exposure of larvae of Xenopus laevis to concentrations of 100, 250, 500, 1000, and 2000 ug/ml for 48 hours induced dose-dependently developmental toxicity (shortened body with wavy fins). Affected larvae were frequently accompanied by abnormal body flexure and edema in the fin. Light microscopy revealed severe damage in the myotome and neural tube; damage of the epidermal tissue was seen at higher concentrations. The highest concentration was completely lethal.

Test substance: caffeine

31-AUG-2000 (634)

Type: other: teratogenicity in vitro

Remark: The teratogenicity of the test substance was evaluated in the Frog Embryo Teratogenesis Assay - Xenopus (FETAX), a 96-hour whole embryo developmental toxicity screening assay.

LC50 was in the range of 0.22 to 0.37 mg/ml.

Test substance: caffeine

23-AUG-2000 (635)

Type: other: teratogenicity in vitro

Remark: The effects of an embryotoxic dose of the test substance on the ultrastructure and mitochondrial function of the embryonic heart was studied in chick embryos. Doses of 1.0 to 4.7 mg were applied to extraembryonic membranes through an observation window of white Leghorn eggs. Abnormalities in the ultrastructure of embryonic cardiocytes (disruption of mitochondrial christae and marked intracellular edema) and inhibition of the mitochondrial succinate oxidation was noted aftr application of 3.5 mg. Increased heart rate (up to 30%), stroke volume, ejection fraction and cardiac output was observed.

Test substance: caffeine

23-AUG-2000 (636) (637)

Type: other: teratogenicity in vitro

Remark: Cultures of whole embryos from RAI rats (explanted on day 9.5 of gestation) were treated in vitro with the test substance at concentrations of 30, 100, 300, and 600 ug/ml in the presence of Aroclor-incuced rat liver S-9 mix. Malformations (hypoplasia of the telencephalon, malformed mandibular aches, reduced somite number, reduced crowm-rump length, and reduced yolk sac size) was seen even at the lowest concentration (Cicurel and Schmid, 1988).
Studies conducted in the presence and absence of a metabolic acivation system showed that the induced malformations occurred at much lower concentrations when a liver microsomal system (S-9 and NADP) was present (Schmid and Cicurel, 1987)

Test substance: caffeine

31-AUG-2000 (638) (639)

Type: other: teratogenicity in vitro

Remark: The teratogenicity of the test substance was studied in the Frog Embryo Teratogenicity Assay - Xenopus (FETAX) in the presence of metabolic activation system (MAS). The 4-day LC50 (median lethal concentration) EC50 (malformation and

MCIG (Minimum Concentration to Inhibit Growth) was calculated.
LC50 = 0.48 mg/ml in the presence of MAS
LC50 = 0.18 mg/ml in the absence of MAS
EC50 = 0.12 mg/ml in the presence of MAS
EC50 = 0.08 mg/ml in the absence of MAS
MCIC = 0.05 mg/ml in the presence of MAS
MCIC = 0.01 mg/ml in the absence of MAS
The result was judged to be positive.

Test substance: caffeine

31-AUG-2000 (640)

Type: other: teratogenicity in vitro

Remark: The aim of the study was to evaluate an in vitro teratogenicity model. Swiss Webster mouse embryos were excised on day 11 of gestation, hindlimb buds were dissected and cultured. After 24 hours of culture, the test substance (50 - 1000 ug/ml) was added for 96 hours. 3H-Thymidine and 35S-sulfate were added after treatment for 72 hours. Teratogenic activity was measured by determining the incorporation of radioactivity. Preferential inhibition of proteoglycan or DNA-synthesis was judged to be indicative of teratogenicity. According to the authors, a significant inhibition of 35S incorporation into sulfated proteoglycan and 3H-thymidinde incorporation into DNA was noted, indicative of depressed cartilage proteoglycan synthesis. The test substance was judged to be positive in this assay.

Test substance: caffeine

23-AUG-2000 (641)

Type: other: teratogenicity in vitro

Remark: The test substance gave positive results in the hydra assay (in vitro developmental toxicity prescreen).

Test substance: caffeine

31-AUG-2000 (642) (643)

Type: other: teratogenicity in vitro

Remark: The vaccina virus test was used as a model system for teratology testing. Strain western reserve was grown in primate cell cultures (vehicle: medium). According to the author, this assay was determined to be 92% sensitive, specific and accurate in predicting rodent teratology. The RD50 was the dose which inhibited or stimulated virus growth by 50%. Positive results were obtained for the test substance. RD50 was 200 ug/ml.

Test substance: caffeine

24-AUG-2000 (644)

Type: other: teratogenicity in vitro

Remark: Cultured fetal palates prepared from gestation day 12.5 ICR mice were incubated with the test substance at concentrations of 0.5, 1, and 2 mM (ca. 97, 194, 388 ug/ml) for 72 hours (vehicle: ethanol). The stage of palatal fusion was evaluated by microscopy. No substance-related effect was seen at the low and mid concentration. At 2 mM, palatal development was inhibited.

Test substance: caffeine

31-AUG-2000 (645)

Type: other: teratogenicity in vitro

Remark: The teratogenic activity of the test substance was studied in cultures of whole chick and rat embryo as well as aggregating embryonic brain cell cultures.
Whole chick embryos were preincubated with the test substance and allowed to develop for another 3 days. Anomalies noted were brain vesicles, branchail region, somites irregular/opposited heart. An IC50 value of 0.3 mmol/l (ca. 58 ug/ml) was established. The test substance showed weak teratogenic potential.
Whole rat embryos were explanted at gestation day 9.5 and incubated with the test substance for 48 h. At a concentration of 0.3 mmol/l (ca. 58 ug/ml), microtelencephalia was noted. Predominant abnormality was hypoplasia of the telencephalon and of the branchial region. The test substance was weakly teratogenic.
Aggregating brain cell cultures were treated with the test substance for 5 to 14 days. At a concentration of 1 mmol/l (ca. 194 ug/ml), decreased levels of 2',3'-cyclic nucleotide c-phosphohydrolase (CNP) were observed.
Based on these results, the test substance was classified as positive with regard to teratogenicity.

Test substance: caffeine

31-AUG-2000 (646)

Type: other: teratogenicity in vitro

Remark: The teratogenic activity of the test substance was studied using a standardized chick embryo culture. Eggs were preincubated for 20 hours. Test solutions were mixed with egg albumin (1:1) prior to application; growth and morphogenesis of the embryos were evaluated after 42 hours. Normal survival was noted at up to 0.1 mM (ca. 19 ug/ml). Anomalies and malformations in 50% of the embryos were present at 0.7 mM (ca. 136 ug/ml). Perturbations in the extraembryonic membrane were noted at 1 mM (ca. 194 ug/ml). Embryonic growth was affected at 5 mM (ca. 970 ug/ml). Data on mortality revealed an LD50 of 4 mM (ca. 777 ug/ml) and an LD100 of 5 mM (ca. 970 ug/ml).
Based on these results, the test substance was classified as positive with regard to teratogenicity.

Test substance: caffeine

31-AUG-2000 (647)

Type: other: teratogenicity in vitro

Remark: The teratogenic activity of the test substance was studied using chick embryos in vitro. Eggs were incubated at 37.5 degree Centrigrade. The embryos at the stage of gastrulation were explanted from the egg into transparent silicon chambers where they continued to develop for 3 days. The test substance was tested in this culture. Survival scores, growth perturbations and early signs of anomalies of the nervous, skeletomotor and cardiovascular systems were noted. Cardiovacular anomalies probably linked to an incomplete torsion and shortening of the cervicothoraic region was seen. LD50 was 623 ug/ml; malformations in 50% of the embryos occurred at 60 ug/ml.
Based on these results, the test substance was classified as positive with regard to teratogenicity.

Test substance: caffeine

31-AUG-2000 (648)

Type: other: teratogenicity in vitro

Remark: In toto mouse embryos were cultivated at embryonic day 8.5 and were incubated with the test substance (105, 310, 620 uM; ca. 20, 60, 120 ug/ml) for 26 h. According to the authors, the doses selected corresponded to concentrations transferred by the placenta of heavy caffeine consumers. Failure of neural tube closure, excessive proliferation of the neuroepithelial cells and premature evagination of telencephalic vesicles were present in 50% of the embryos. When reaching the embryonic neural tube before neuronal migration, the test substance modified the schedule and/or the rate of neuronal proliferation.

Test substance: caffeine

31-AUG-2000 (649)

Type: other: teratogenicity in vitro

Remark: A short-term screening test for teratogens was evaluated. The ability of the test substance to interfere with morphological differentiation in mouse neuroblastoma cells (N1E-115 clone) was studied (vehicle: water or ethanol). No substance-related effect was seen at a concentration of 0.01 mM (ca. 1.9 ug/ml). Differentiation of the cells was induced at a concentraion of 0.1 mM (ca. 19.4 ug/ml).

Test substance: caffeine

24-AUG-2000 (650)

Type: other: teratogenicity in vitro

Remark: The stem-cell test, an in vitro teratogenicity assay was validated. Embryonic stem cell line D3 was incubated with

the test substance for 7 days. Effects on cell survival (cytotoxicity) and differentiation were measured. The criterion for classification as a teratogen was specific inhibition of cell differentiation, i.e. materials were classified as positive if the ratio (A/D) of the IC50 for cytotoxicity (A) to the IC50 for differentiation (D) exceeded 2. The sensitivity of this test was 73%, its specificity was 70%
With caffeine, IC50 for cytotoxicity was 78 ug/ml; IC50 for differentiation was 68 ug/ml, resulting in an A/D ration of 1.15.

Test substance: caffeine

31-AUG-2000 (651)

Type: other: teratogenicity in vitro

Remark: The teratogenic potential of the test substance was determined in an in vitro screening assy using growth inhibition of human embryonic cells. The ability of the test substance to inhibit the growth of human embryonic mesenchymal cells was studied at a concentration of 1 mM (ca. 194 ug/ml); vehicle was medium, water, ethanol or DMSO. No effect of the test substance was found.

Test substance: caffeine

31-AUG-2000 (652)

Type: other: teratogenicity in vitro

Remark: The teratogenicity of the test substance was studied using limb bud cell cultures. Embryos were removed from Sprague-Dawley dams on day 13 of gestation.; limb buds were removed and cultured. The cells were incubated with the test substance at five different concentrations for 5 days. Cell differentiation was quantified spectrophotometrically. The test substance was classified as a positive specific inhibitor of proloferation at concentrations of 100-1000 ug/ml.

Test substance: caffeine

24-AUG-2000 (653)

Type: other: teratogenicity in vitro

Remark: The teratogenicity of the test substance was evaluated in the Frog Embryo Teratogenesis Assay: Xenopus (FETAX). Groups of 20 normally developing mid-cleavage blastulae from female Xenopus were continuously exposed to the test substance at concentrations of 0-100 ug/ml for 96 hours. Mortality and stage of development were checked at 24, 48, 72 and 96 hours. Remaining endpoints, including LC50, EC50 (malformation-teratogenesis), NOEC, growth, motor behaviour, pigmentation and gross anatomy were recorded at 96 hours. Teratogenicity index (TI50) was determined. According to the authors, TI50 was > 2.5, representative of a high potential for teratogenicity.

Test substance: caffeine

31-AUG-2000 (654)

Type: other: teratogenicity in vitro

Remark: The teratogencity of the test substance was tested in the embryonic stem cell test using BALB/c 3T3 fibroblasts and D3ES embryonic stem cells. The cells were incubated with the test substance (155-795 ug/ml) for 1, 3, and 10 days. The MTT assay was used to assess cytotoxicity in both cell lines. Inhibition of differentiation was measured in the D3ES cells. According to the authors, the stem cells were

slightly more sensitive to caffein than the adult 3T3 cells.

Test substance: caffeine

31-AUG-2000 (655)

6.1 Analytical Methods

6.2 Detection and Identification

7.1 Function

7.2 Effects on Organisms to be Controlled

7.3 Organisms to be Protected

7.4 User

7.5 Resistance

8.1 Methods Handling and Storing

Fire/Exp. Prot.: prevent electrostatic charge - sources of ignition should be kept well clear - fire extinguishers should be kept handy
Storage Req.: Keep tightly sealed. Protect from light.
Transport Code: Not classified as hazardous under transport regulations.

Remark: PERSONAL PROTECTIVE EQUIPMENT

Respiratory protection: dust mask

Hand protection: protective gloves

Eye protection: Wear eye/face protection.

General safety and hygiene measures: The usual precautions for thehandling of chemicals must be observed.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

8.2 Fire Guidance

Ext. Medium: water, dry extinguishing media, carbon dioxide (CO2), foam
Add. Information: Dispose of fire debris and contaminated extinguishing water in accordance with local regulations.
Products arising: unknown

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

8.3 Emergency Measures

Type: other: general advice

Remark: Remove contaminated clothing.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

Type: injury to persons (skin)

Remark: Wash with soap and water.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

Type: injury to persons (eye)

Remark: Immediately wash affected eyes for at least 15 minutes under running water with eyelids held open, consult an eye specialist.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

Type: injury to persons (oral)

Remark: Immediately rinse mouth and then drink plenty of water, summon physician.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

Type: injury to persons (inhalation)

Remark: keep patient calm, remove to fresh air, summon medical help
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

Type: accidental spillage

Remark: Personal precautions: Ensure adequate ventilation.

Environmental precautions: Do not let product enter drains. Prevent product from entering water courses or the ground.

Methods for cleaning up: Sweep up and then dispose of.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

8.4 Possib. of Rendering Subst. Harmless

8.5 Waste Management

Memo: other: Must be disposed of by special means, e.g. suitable incineration, in accordance with local regulations.

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material

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10.1 End Point Summary

10.2 Hazard Summary

10.3 Risk Assessment