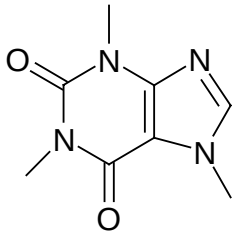
SIDS INITIAL ASSESSMENT PROFILE

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.