FOREWORD INTRODUCTION

THEOPHILLINE

CAS N°: 58-55-9

SIDS Initial Assessment Report for SIAM 13

(Bern, Switzerland, November 2001)

1. Chemical Name:	**Theophylline**
2. CAS No.:	**58-55-9**
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn- Bad Godesberg
4. Shared Partnership With:	
5. Roles/Responsibilities of the Partners: • 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 OECD HPVChemicals Program?	by ICCA-Initiative
7. Review Process Prior to the SIAM:	last literature search (update): 5 June 2001 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 26 April 2001 (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:	14. September 2001
10. Comments:	

OECD/ICCA - The BUA[1] 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)

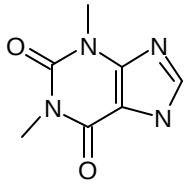
- **Review of validity of structure-activity relationships**

- **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.**

[1] BUA (GDCh – Beratergremium fuer Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	58-55-9
Chemical Name	Theophylline
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Theophylline is moderately toxic after oral uptake and low toxic after dermal and inhalative uptake. LD50, rat (oral): 272 mg/kg bw, LC50, rat (inhalation, aerosol): >6.7 mg/l/4h, LD50, rat (dermal): >2000 mg/kg bw. Main symptoms following exposure are convulsion and accelerated respiration (oral) and irregular and accelerated respiration (inhalation). The undiluted substance was not irritating to the eyes. The substance in a 50% aqueous dilution was not irritating to the skin of rabbits. In repeated dose studies, theophylline was given to rats and mice by feed or by gavage. In rats theophylline caused nephropathy in all fed male rats and a dose-dependent periart eritis in all treated groups. Those effects are discussed to be secondary effects, due to the pharmacological properties (vasodilatation/ -constriction) of methylxanthines. No histo-pathological changes were found in other organs including sex organs of rats and mice. LOAEL: 75 mg/kg bw/d (rat, feed), 37.5 mg/kg bw/d (rat, gavage), LOAEL: 175 mg/kg bw/d (mouse, male, feed), 225 mg/kg bw/d (mouse, female, feed), NOAEL: 75 mg/kg bw/d (mouse, male, gavage), 150 mg/kg bw/d (mouse, female, gavage). Theophylline was not mutagenic or clastogenic in most of the standard *in vitro* tests. Positive results were found only at high, cytotoxic concentrations and without metabolic activations. Theophylline had no mutagenic or clastogenic effects *in vivo*.

In fertility/developmental toxicity studies in mice, the oral administration of theophylline resulted in changes in parental body weight and significant reproductive effects to the offspring (reduced mean number of litters, fewer live pups per litter, decreased live pup weight). No effects were observed in sperm morphology or in the estrous cycle in rats and mice in 14 week studies. LOAEL: 126 mg/kg bw/d. Theophylline was not shown to be teratogenic in CD-1 mice at oral doses up to 396 mg/kg bw/d or in CD-1 rats at oral doses up to 259 mg/kg bw/d. At an oral dose of 218 and 396 mg/kg bw/d, fetotoxicity was observed in rats and mice, respectively, in the presence of maternal toxicity. Intravenous theophylline was fetotoxic and teratogenic in rabbits at maternal toxic doses exceeding the effective therapeutic range (60 mg/kg bw/d i.v.). NOAEL rat maternal/fetotoxicity: 124 mg/kg bw/d, NOAEL rat teratogenicity: 259 mg/kg bw/d. NOAEL mouse maternal/fetotoxicity: 282 mg/kg bw/d, NOAEL mouse teratogenicity: 396 mg/kg bw/d. NOAEL rabbit maternal/fetotoxicity/teratogenicity: 30 mg/kg bw/d. Theophylline showed no carcinogenic activity in rats and mice when tested up to the highest doses (75 mg/kg bw/d rats, female mice and 150 mg/kg bw/d male mice).

In rats theophylline is rapidly and completely absorbed from the digestive tract and distributed to all organs except adipose tissue. It readily crosses the placenta and no blood-brain barrier was observed. Plasma half-life is between 1.2-4 hours in rats and 6-11.5 hours in dogs and strongly dependent on protein binding and dose. Theophylline is metabolized in the liver, mainly by the microsomal system. The metabolites are excreted into the bile and eliminated with the urine. In humans theophylline is readily absorbed after oral intake and distributed in the different body tissues and breast milk. Theophylline is metabolized in the liver and excreted by the kidney. Only 7-12 % is excreted unchanged in the urine. Major metabolites are 1,3-dimethyluric acid (35-55 %), 1-methyluric acid (13-26 %) and 3-

methylxanthine (9-18 %). The elimination half-time is 3-11 hours in adults. Signs of intoxication are: headache, gastrointestinal disturbances, hypotension, irritability and insomnia, tachycardia, arrhythmia, cardiac arrest and serious neurological symptoms. Seizures and death have also occurred. Toxicity may be developed at serum levels of 20-30 µg/ml, whereas at levels below 15 µg/ml generally no symptoms were observed. Case-control studies did not show an association between total methylxanthine intake and benign breast disease or breast cancer. No association with congenital abnormalities or stillbirth were seen in studies with females receiving theophylline. In premature infants no effect of theophylline on the development was seen.

Environment

Theophylline has a water solubility in the range of 5.5 to 8.3 g/l, a vapor pressure of $0.7 * 10^{-6}$ Pa and a log Kow of –0.0076. Distribution modelling using Mackay, Level I, indicates that the main target compartment will be water with 99,98%. According to OECD criteria the substance is readily biodegradable. The calculated hydrolysis rate is extremely slow. In the atmosphere theophylline will be indirectly photodegraded by reaction with hydroxyl radicals with a half-life of 20 hours (calculated). Bio- and geoaccumulation is not expected according to the log Kow (-0.0076).

The acute aquatic toxicity has been determined for fish (*Leuciscus idus* LC50(96h) appr. 100 mg/l), for aquatic invertebrates (*Daphnia magna* EC50(48h) 178 mg/l) and for algae (*Scenedesmus subspicatus* EC50(72h) >100 mg/l). Based on these acute toxicity studies theophylline is not considered as hazardous to aquatic organisms. Results from prolonged or chronic studies are not available. Following the EU risk assessment procedure, the PNEC aqua can be calculated to 0.1 mg/l by applying an assessment factor of 1000 on the most sensitive species (*Leuciscus idus* LC50(96h) 100 mg/l).

Exposure

Theophylline is produced with a volume of 1,000 to 5,000 tons per year, world-wide, the same level accounting for Germany and Europe. Theophylline is a substance with wide disperse use. It is predominantly used as an antiastmathic drug in the pharma sector (99%). 1% is used in cosmetic applications. Production sites for the technical product: EU (Germany) 1, NAFTA 1, India 1 and China 5. Furthermore theophylline is a naturally occurring substance in plants e.g. in black tea (200 – 400 mg/kg dry weight), coffee (approx. 5 mg/kg in green coffee beans) and cocoa (trace amounts) and therefore is a component in the respective beverages. The use in pharmaceutical applications and also the use in foods will be the predominant way of human exposure and of exposure of the environment. Exposure of workers to theophylline during production is adequately controlled in the industry of the sponsored country. Workplace measurements Germany: 0.1- ca. 0.5 mg/m^3 (8h). At the German production site, process waters with relevant substance quantities are separated and combusted.

NATURE OF FURTHER WORK RECOMMENDED

The substance is currently of low priority of further work. However there is a recommendation for sharing the information on possible aggregated exposure with regulatory agencies responsible for food, pharmaceuticals and cosmetics.

FULL SIDS SUMMARY

CAS NO: 58-55-9		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			270 – 274 °C
2.2	Boiling Point			Not relevant because of chemical decomposition
2.3	Density		Bulk density	500 kg/m^3 at 20°C
2.4	Vapour Pressure		calculated	0.0000007 Pa at 25 °C
2.5	Partition Coefficient (Log Kow)		measured	-0.0076 at 23°C
2.6	Water Solubility			5,500 - 8,300 mg/l at 20 °C
	pH			4 – 6 at 20 g/l and 20 °C
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		calculated	Indirect photolysis: air Reaction with OH-radicals: $t_{1/2}$ = 20 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 99.98 % In air, sediment, soil and biota <0.1%
3.5	Biodegradation		OECD 301 A	readily biodegradable (90-100% after 22 days)
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	Leuciscus idus	DIN 38 412 part 15	LC50 (96 hours) = appr. 100 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates	Daphnia magna	OECD 202	EC50 (48 hours) = 178 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	Scenedesmus subspicatus	OECD 201	ErC50(72h) >100 mg/l ErC10 (72h) > 100 mg/l EbC50 (72 h) > 100 mg/l EbC10 (72 h) = 18.4 mg/l NOEC (72 h) = 12.5 mg/l
4.4	Toxicity to bacteria	Pseudomonas putida	DIN 38412 part 8	EC50 (17 hours) 2,110 mg/l
	Inhibition of activated sludge		OECD 209	EC20 (3 hours) appr. 900 mg/l
4.6.2	Toxicity to Terrestrial Plants	Oryza sativa		Growth inhibition at 2.5 mM

CAS NO: 58-55-9		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Comparable to OECD guideline 401	LD50 = 272 mg/kg bw
5.1.2	Acute Inhalation Toxicity	Rat	OECD 403	LC50 > 6.7 mg/l/4h (aerosol)
5.1.3	Acute Dermal Toxicity	Rabbit	Comparable to OECD guideline 402	LD50 > 2000 mg/kg bw
5.4	Repeated Dose Toxicity	Rat	14 weeks, feed, NTP program	LOAEL 75 mg/kg bw
		Rat	14 weeks, ,gavage, NTP program	LOAEL 37.5 mg/kg bw
		Mouse	14 weeks, feed, NTP program	LOAEL 175 mg/kg bw males, LOAEL 225 mg/kg bw females
		Mouse	14 weeks, gavage, NTP program	NOAEL 75 mg/kg bw males NOAEL 150 mg/kg bw females
5.5	Genetic Toxicity *In Vitro*			
	Bacterial Test (Gene mutation)	*Salmonella typhimurium*	Comparable to OECD guideline 471	Negative (with and without metabolic activation)
	Non-Bacterial *In Vitro* Test (Chromosomal aberrations)	CHO cells	Comparable to OECD guideline 473	Negative (with and without metabolic activation)
	mouse lymphoma assay	L5178Y cells	Comparable to OECD guideline 476	Negative
5.6	Genetic Toxicity *In Vivo*	Mouse	Cytogenetic assay, i.p. Comparable to OECD guideline 475	Negative
		Mouse	Micronucleus, 14 weeks, feed and gavage. Comparable to OECD guideline 474	Negative
		Rat	Cytogenetic, 75 weeks, spermatogonia Comparable to OECD guideline 483	Negative
5.8	Toxicity to Reproduction	Rat	Continuous breeding, feed 18 weeks, NTP program	LOAEL 126 mg/kg bw, adverse reproductive effects in absence of maternal toxicity
5.9	Developmental Toxicity/ Teratogenicity	Rat	Feed, day 6-15, NTP program	NOAEL maternal/fetotoxicity 124 mg/kg bw NOAEL teratogenicity 259 mg/kg bw
		Mouse	Drinking water, day 6-15, NTP program	NOAEL maternal/fetotoxicity 282 mg/kg bw NOAEL teratogenicity 396 mg/kg bw/d
		Rabbit	i.v. application	NOAEL maternaltoxicity / treatogenicity/fetotoxicity 30 mg/kg bw/

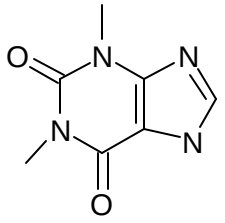
CAS NO: 58-55-9		SPECIES	PROTOCOL	RESULTS
Further Data	Corrosiveness/Irritation Skin	Rabbit	OECD 404	Not irritating, (50% aquous solution was tested)
	Corrosiveness/Irritation Eye	Rabbit	OECD 405	Not irritating
	Carcinogenicity	Rat	Gavage, 2 years, up to 75 mg/kg bw, NTP program	Negative
		Mouse	Gavage, 2 years, up to 150 mg/kg bw, NTP program	Negative
5.11	Experience with Human Exposure		Kinetics:	Readily absorbed and distributed through the body tissues; elimination half-time 3-11 hrs.
			Signs of intoxication:	Headache, gastrointestinal disturbances, hypotension, irritability, arrhythmia, seizures and death;
			Case-control studies:	No association with benign breast disease or breast cancer; No association with congenital abnormalities or stillbirth were seen in studies with females receiving theophylline. Theophylline had no effects on the development of premature infants.

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

Chemical Name: Theophylline
Synonyms: 3,7- Dihydro-1,3-dimethyl-1H-purine-2,6-dione
1,3-Dimethyl-2,6-Dioxo-1,2,3,6-tetrahydropurin
1,3-Dimethylxanthine

CAS Number: 58-55-9
Empirical Formula: $C_7 H_8 N_4 O_2$
Structure:



General Substance Information

Substance type: organic
Physical status: solid
Purity: 97 - 100 % w/w

Physical and chemical properties

Theophylline is soluble in water with a range of 5.5 to 8.3 g/l at 20 °C (BASF AG, 2001a) and has a calculated vapour pressure of 0.0000007 Pa at 25 °C (BASF AG 2000a). The partition coefficient log P_{ow} is measured to –0.0076 at 23 °C (BASF AG 1988a). The melting point is 270 – 274 °C (Merck Index 1989).

2. GENERAL INFORMATION ON EXPOSURE

1999 the estimated world production of theophylline amounts to 1,000 – 5,000 tons, the same level accounting for Germany and Europe.
Production sites for the technical product are:
EU (Germany) 1, NAFTA (USA; Canada, Mexico) 1, India 1 and China 5.
Theophylline is a substance with wide disperse use. It is predominantly used as an antiasthmatic drug in the pharma sector (99%). 1% is used in cosmetic applications. Theophylline concentrations in cellulite reduction creams are below 1% (BASF AG 2001c).
Furthermore, theophylline is a naturally occurring substance in plants e.g. black tea (200 – 400 mg/kg dry weight), coffee (appr. 5 mg/kg in green coffee beans) and cocoa (trace amounts)(The Merck Index 1989).

Releases into the environment may occur during production of theophylline, during formulation and use of pharmaceuticals.

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). No release data are available for other production sites.

Distribution modelling using Mackay, Level I, indicates that the main target compartment will be water with 99.98% (BASF AG 2000a).

Theophylline is indirectly photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 20 hours (calculated) (BASF AG 2000a). According to OECD criteria the substance is readily biodegradable. (OECD 301 A, 90 - 100 % after 22 days, >90% at the end of the 10-days-window) (BASF AG 2000c). The calculated hydrolysis rate is extremely slow ($T_{1/2}$ >1 year) (BASF AG 2000a).

The estimated soil adsorption coefficient (log K_{oc} –0.2319) suggests that theophylline would not adsorb to soil particles (BASF AG, 2000a). No experimental data on bioaccumulation are available. The log K_{ow} of –0.0076 indicates no potential for bioaccumulation.

2.2 Human exposure

Exposure of workers to theophylline during production is adequately controlled in the industry of the sponsor country (Germany).
Theophylline is produced under controlled conditions in closed systems. Exposure may only occur during occasional filter changes. During this operation, dust masks, one way protective suits, and gloves are worn.
Workplace measurements (during filter changes), Germany: 0.1- ca. 0.5 mg/m^3 (8h)
In the formulation of tablets local ventilation systems are used, and most formulation steps take place in closed systems. Hence, there is practically no exposure under normal workplace conditions.

3. HUMAN HEALTH HAZARDS

3.1 Effects on human health

3.1.1 Kinetics and metabolism

Kinetics and metabolism of theophylline in **animals** have been reviewed by IARC, (1991). It is rapidly and completely absorbed from the digestive tract and distributed to all organs of rats except adipose tissue. It readily crosses the placenta and no blood-brain barrier was observed in fetal rats. Plasma half-life is between 1.2-4 hours in rats and 6-11.5 hours in dogs and strongly dependent on protein binding and dose. Theophylline is metabolized in the liver, mainly by the microsomal system. The metabolites are excreted into the bile and eliminated with the urine.
Theophylline is metabolized similarly in animals and man and the same main metabolites are produced, though there are some quantitative differences between species

In **humans**, theophylline is readily absorbed after oral intake. The absorbed fraction of a dose of approx. 7.5 mg/kg bw averaged 99 % *(Hendeles et al. 1977)*. Absorption rate and absorbed amount can be altered by food intake *(Welling et al. 1975)*. Peak serum levels were reached within 0.5-2 h *(Hendeles et al. 1977, Ogilvie 1978)*.

About 50% of theophylline is bound reversibly to plasma proteins *(Aranda et al.* 1976, *Ogilvie 1978)*. Theophylline is distributed in erythrocytes *(Mitenko and Ogilvie 1973)*, saliva *(Culig et al. 1982)* and breast milk *(Yurchak and Jusko 1976)*, and can cross the placenta *(Arwood et al. 1979)* and the blood-brain barrier *(Kadlec et al. 1978)*. The apparent volumes of distribution averages 0.5 l/kg bw *(Ogilvie. 1978, Aranda et al, 1976)*.

The elimination half-time is 3-11 hours in adults *(Jenne et al. 1972, Hunt et al. 1976, Chrzanowski et al. 1977)*. Elimination half-time is shorter in smokers and is prolonged by the use of oral contraceptives *(Jenne et al. 1975, Hunt et al. 1976, Tornatore et al, 1982, Roberts et al, 1983)*.

Theophylline is metabolized by ring oxidation and N-demethylation mediated by microsomal enzymes (cytochrome P-450) in the liver and is excreted by the kidney. Major metabolites are 1,3-dimethyluric acid (35-55 %), 1-methyluric acid (13-26 %) and 3-methylxanthine (9-18 %). Only 7-12 % is excreted unchanged in the urine *(Lesko 1986, Tang-Liu and Riegelman. 1981, Birkett et al. 1985)*.

Dose-dependent pharmacokinetics are seen with plasma concentrations greater than 15 µg/ml *(Weinberger and Ginchansky, 1977)*. Nonlinearity may be due to metabolic saturation of hepatic metabolism and changes in the renal clearance *(Lesko 1986)*.

In neonates, methylation into caffeine is the predominant metabolic pathway *(Bory et al. 1979)*. Methylation occurs also in adults *(Tang-Liu and Riegelman 1981)*.

Elimination is modified by diet. High protein diet resulted in enhanced elimination *(Feldman et al. 1980, Anderson et al. 1979)*. Studies in twins showed large interindividual variations *(Miller et al. 1985)*.

The pharmacokinetics of theophylline vary widely among similar patients and cannot be predicted by age, sex, body weight, or other demographic characteristics. In addition, certain concurrent illnesses and

alterations in normal physiology and co-administration of other drugs can significantly alter the pharmacokinetic characteristics of theophylline. Theophylline interacts with a wide variety of other drugs.

3.1.2 Acute Toxicity

After oral application, the LD_{50} for rats (10 animals/group/sex) was found to be 272 mg/kg bw; as clinical symptoms of toxicity clonic convulsions, accelerated respiration and salivation (at 1000 mg/kg only) were seen after oral intake (Knoll AG 1983). Higher doses can be tolerated when the substance is not given as a bolus.
The inhalation of the substance by rats as an aerosol over the time period of 4 h resulted in an LC_{50}-value of > 6.7 mg/l. Irregular and accelerated respiration were noted in this study (BASF AG 1989).
The LD_{50} for dermal application was >2000 mg/kg bw; no clinical symptoms were observed (BASF AG 1988)

Conclusion: In animal studies theophylline showed a moderate toxicity after oral uptake and a low acute toxicity after dermal and inhalative uptake.

3.1.3 Corrosiveness and Irritation

In tests performed according to OECD guidelines 404 and 405 in rabbits, the undiluted substance induced mean scores of 0.6 for cornea opacity , 1.8 for conjunctival redness, and 0.6 for swelling. On day 8, one of 3 animals showed opacity grade 1 and conjunctivitis grade 2. The animal showing slight corneal opacity had also keratitis. The effects could possibly be due to mechanical irritation by the crystalline test substance.

The substance in a 50% aqueous dilution was not irritating to the skin (score 0) (BASF AG 1985).

Conclusion: The undiluted substance was not irritating to the eyes. The substance in a 50% aqueous dilution was not irritating to the skin of rabbits

3.1.4 Repeated Dose Toxicity

Male and female F344/N rats and B6C3F1 mice were given theophylline in feed or in corn oil by gavage for 16 days or 14 weeks or in corn oil by gavage for 2 years (NTP 1998, Collins1988. Lindamood III et al. 1988). For the results of the 2 yr-study, cf. section 3.1.8 “carcinogenicity”.

Feeding study with rats - 14 weeks
Rats were fed diets containing the substance at doses of 0, 1000, 2000 and 4000 ppm (ca. 75, 125, and 250 mg/kg bw/d for male rats; ca. 75, 125, and 275 mg/kg bw/d for female rats). Each group consisted of 10 animals/sex.
There were no mortality or significant weight-gain depression in any of the treated groups. The food consumption was unaffected. No substance-related gross lesions were observed. Mean cell volume of red blood cells and mean cell hemoglobin of red blood cells was increased in mid dose and high dose males. The platelet count of high dose males was increased. Segmented neutrophil counts were increased in all females fed the substance.
A dose-dependent increase in the incidence of mesenteric and/or pancreatic periarteritis was observed in the mid and high dose group of males (2 and 3 animals respectively) and in all dose groups of females (1, 1, 5 animals).

Periarteritis was characterized by infiltration of mononuclear and polymorphonuclear leukocytes into the media and adventitia, and the more severe lesions included degeneration of medial smooth muscle and periarterial fibrosis. These effects were also observed in the gavage dose-finding study after 16 days in males of the highest dose group (400 mg/kg bw/d) and in the 2-year study in males of the highest dose group (75 mg/kg bw/d) (see 3.2.8). Theophylline is a non-specific phosphodiesterase inhibitor, which may cause excessive vasodilatation. The mesenteric and pancreatic arteries in rats are particularly sensitive to the excessive vasodilator-pharmacological activity of theophylline, caffeine and other vasodilator drugs. The periarteritis may be a consequence of hemodynamic changes induced in the vascular wall (Nyska et al. 1998).

Kidney weights were increased in males fed 250 mg/kg bw/d. A nephropathy, characterized by randomly distributed foci of tubular degeneration, dilated tubules containing eosinophilic protein casts and focal interstitial mononuclear cell infiltrates was observed in all males, including the controls. The severity of lesions progressed with dose (controls and low dose: minimal, mid-dose: mild, high-dose: moderate). The mechanism of this effect is unclear, it may relate to the fact that theophylline, as well as other xanthines, acts as a potent vasoconstrictor in the kidney, in contrast to all other vascular beds in which these compounds induced vasodilation (Osswald 1983, Williams 1987). However, also the relevance of this finding is unclear, since these effects (though less severe) have also been observed in the controls, but were not found in other repeated dose studies with theophylline.

No significant differences were found between control and exposed rats in sperm morphology, and in vaginal cytology parameters nor at the microscopic evaluation of sex organs (NTP 1998, Collins 1988).

LOAEL rat, oral feed, 14 weeks: 75 mg/kg bw/d (nephropathy (m); periarteritis (f))

Gavage study with rats – 14 weeks

Rats were administered 0, 37.5, 75, and 150 mg/kg bw/d in corn oil. Each group consisted of 10 animals/sex.

One high-dose male rat and one high-dose female died before the end of the study. The mean body weight gain of the 150 mg/kg bw/d females was significantly greater than that of the controls. Food consumption of high-dose females and high-dose males appeared to be slightly higher than that of the control group. No treatment-related gross observations were noted at necropsy. Several organ weight changes were found in an unspecific manner. Thymus weights were decreased in high dose rats, and liver weights were increased in mid and high dose females. The observed findings had no histopathological correlations.

Microscopic examinations revealed a slight dose-dependent increase in the incidence of periarteritis of the small- to medium-size arteries adjacent to the mesenteric lymph nodes of male and female rats (periarteritis incidences males: control 1/10, 37.5: 1/10, 75: 2/10; 150: 5/10; females: 0/10, 2/10, 2/10; 3/10). The periarteritis observed in 1 control male was more consistent with that commonly observed in aged rats and consisted of minimal, focal lymphocytes accumulation adjacent to the artery. The periarteritis was focal or circumferential and was characterized by infiltration of mononuclear and polymorphonuclear leukocytes into the media and adventitia. As described above the periarteritis may be a consequence of hemodynamic changes induced in the vascular wall.

Mean cell volume of red blood cells was increased in high dose males and mean cell hemoglobin of red blood cells was increased in all treated males. No significant differences were found between control and exposed rats in sperm morphology, and in vaginal cytology parameters nor at the microscopic evaluation of sex organs (NTP 1998, Collins1988).

LOAEL rat, gavage, 14 weeks: 37.5 mg/kg bw/d (periarteritis)

Feeding study in mice – 14 weeks

Mice were fed diets containing the substance at doses of 0, 1000, 2000 and 4000 ppm (ca. 175, 400, and 800 mg/kg bw/d for male mice; ca. 225, 425, and 850 mg/kg/d bw for female mice). Each group consisted of 10 animals/sex.

No deaths were observed in the feeding study.

Final mean body weights and body weight gains were reduced in all treated mice as compared to the control. The final weight in comparison to the control was significantly reduced in males by 13%, 15% and 14% and in females by 8%, 7% and 7% in the low, mid and high doses, respectively. Relative thymus weights were decreased in females at mid- and high-dose group.

Leukocyte, segmented neutrophil and lymphocyte counts were increased in high dose males and females and in mid dose females. No significant exposure-related lesions were observed at necropsy. Histological examinations revealed a hepatocyte glycogen depletion in all treated groups, which is considered as a result of lower body weights. No other findings were noted in the inner organs or in the sex organs.

No significant differences in sperm morphology or vaginal cytology parameters were observed between control and exposed mice (NTP 1998, Collins1988). Because of the reduced body weights, a NOAEL could not be achieved.

LOAEL mouse, male, feed, 14 weeks: 175 mg/kg bw/d ;
LOAEL mouse, female, feed, 14 weeks: 225 mg/kg bw/d

Gavage study in mice - 14 weeks

In the gavage study mice received 0, 75, 150, and 300 mg/kg bw/d in corn oil. Each group consisted of 10 animals/sex.

3 high dose males, all high-dose females, one low-dose male, and one control female died.

Final mean body weights and body weight gains were reduced in male mice in the mid and high dose level. Mean cell volume of red blood cells and mean cell hemoglobin increased in males of the 300 mg/kg bw/d dose group. Like in the feeding study hepatocyte glycogen depletion was observed (in females only); lymphoid depletion (minimal to moderate) was observed in the thymus and spleen of high-dose male and was considered to be related to stress associated with theophylline administration. There were no histopathological findings attributed directly to theophylline treatment, no changes were found in the sex organs. No significant differences in sperm morphology nor vaginal cytology parameters were observed between control and exposed mice (NTP 1998, Collins 1988).

NOAEL: mouse, male, gavage, 14 weeks: 75 mg/kg bw/d
NOAEL: mouse, female, gavage, 14 weeks: 150 mg/kg bw/d

Conclusion:

Theophylline was given by feed or by gavage to rats and mice. In rats, theophylline caused nephropathy in male rats in one study and a dose-dependent periarteritis in all treated groups.

Periarteritis was not observed in mice, and in a two-year study in rats this effect only occurred in the males of the highest dose group (75 mg/kg bw/d). The particular sensitivity of rats is most probably due to their anatomical situation as compared to mice and men. Since the periarteritis is considered a rat-specific response to vasodilators it is of little, if any, relevance to humans (Nyska et al. 1998). Furthermore, this effect has not been associated with theophylline treatment in humans (Jung, 2001).

At high doses hematological parameters were changed in mice and rats, histopathological changes were not observed in mice. In these studies no histopathological changes were found in other organs including sex organs of rats or mice.

3.1.5 Genetic Toxicity

3.1.5.1 Genetic toxicology in vitro

The substance was negative in the Ames test (tested up to 10000 µg/plate TA1535, 97, 98, 100) with and without metabolic activation (NTP 1998 and Zeiger et al. 1988). No induction of chromosomal aberrations was observed in CHO cells with and without metabolic activation (tested up to 600 µg/ml; comparable to OECD guideline no 473) (NTP 1998). Also a negative result was described in a mouse lymphoma assay (tested up to 5000 µg/ml; comparable to OECD guideline no 476) (Honma 1999a). In a second mouse lymphoma assay with a longer treatment period of 24h the authors found weakly positive results (no information was given on colony size, therefore, no conclusions can be drawn as to whether the substance caused chromosomal aberrations or gene mutations) (Honma 1999b).
Further in vitro tests have been performed with microorganisms, cell cultures and human lymphocytes, mostly with a negative result. Some positive results were found only at high, cytotoxic concentrations and without metabolic activation systems. Some inconclusive or positive responses were seen in non-validated test systems or in not well documented studies. Hence, these few questionable or positive results were judged not suitable to be taken into account in the overall evaluation.

3.1.5.2 Genetic toxicology in vivo

The substance did not induce chromosomal aberrations in bone marrow cells of mice dosed i.p. with up to 250 mg/kg bw, a dose level that was limited by toxicity (Mc Fee 1991). The substance was negative in the mouse micronucleus test in peripheral blood erythrocytes after oral administration (feed up to 4000 ppm and gavage up to 300 mg/kg bw/d, 14 weeks) (NTP 1998, Witt et al. 2000).
In further tests, no chromosomal aberrations and no inhibition of mitotic ratio were observed in spermatogonial cells of rats treated 75 weeks with 0.5 per cent (ca. 230 mg/kg bw/d) theophylline in the feed (Friedman et al. 1979). Negative results were described in a weakly documented dominant lethal assay after i.p. injection of 380 and 480 mg/kg bw in mice (Epstein et al. 1968 and 1972) and in a host-mediated assay after doses up to 300 mg/kg bw in mice (Gabrige and Legator 1968).
A slight increase of sister chromatid exchanges in bone marrow cells of mice (factor 1.3-1.8 in comparison to the control, no inhibition of cell cycle) was observed after i.p. administration of theophylline up to 250 mg/kg bw (Giri 1999 and Mc Fee 1991).

Conclusion:
Theophylline was not mutagenic or clastogenic in most of the standard *in vitro* tests. Positive results were found only at high, cytotoxic concentrations and without metabolic activations. Theophylline had no mutagenic or clastogenic effects *in vivo*.

3.1.6 Toxicity to reproduction

Theophylline was tested for its effects on reproduction and fertility in CD-1 mice (20/sex per group; controls 40/sex per group) using the Reproductive Assessment by Continuous Breeding (RACB) protocol. Data on food and water consumptions, body weights, and clinical signs during a two week dose-range-finding study (Task 1) were used to set exposure concentrations for the Task 2 (14 weeks) continuous cohabitation study at 750, 1500, and 3000 ppm in feed. Feed consumption was not altered by theophylline addition. These levels gave calculated consumption estimates of nearly equal to 126, 260, and 500 mg/kg bw/d.

Alopecia occurred in both sexes of all groups of treated animals (20-25% in the 126 mg/kg bw/d group, and >50% in the 260 and 500 mg/kg bw/d groups). Seven mice died during Task 2: 3 controls, and 4 in the low dose group. A single control mouse showed alopecia; this was less severe than that seen in the treated mice.

Significant reproductive effects were observed: there was a 19 % reduction in the mean number of litters per pair for the high dose mice, fewer live pups per litter at all doses (reduced by 22 %, 29 %, and 42 % in the low - high dose groups, respectively), and, at the highest concentration level, a 6 % decrease in live pup weight adjusted for litter size. The number of days to deliver each litter was consistently greater in the 500 mg/kg bw/d treated group, being longer by 3 days for the first litter, and by 5 days for the last litter, and similarly increased for all others.

Given the significant effects on reproductive performance, a crossover mating (Task 3) was used in an attempt to identify the affected sex. In this mating trial, there were no differences in the percent of pairs mating, or delivering a live litter.
However, in the group cohabiting control males and 500 mg/kg bw/d exposed females, the proportion of pups born alive was reduced by 16%, and the adjusted live pup weight was reduced by 15%. (The results suggest that the female mice may be more sensitive).

After the litters in Task 3 were delivered, evaluated, and discarded, the females were evaluated for vaginal cyclicity for 7 days, and then the parental (F0) mice in the control and 500 mg/kg bw/d theophylline groups were killed and necropsied. There was a 5% increase in female terminal body weights in the high dose group, and an 11% increase in liver weight adjusted for body weight. Interestingly, there were no changes in the length of the estrous cycle, or in the percent of time spent in the various estrous stages. Treated male terminal body weights were reduced by 7% vs. controls. Body-weight-adjusted seminal vesicle weight decreased by 19%. Epididymal sperm density was reduced by 20% in the high dose group; the percent of motile and of abnormal morphologic forms were unchanged by 500 mg/kg bw/d theophylline exposure.
No second generation analysis was conducted (NTIS 1985a).
The reliability of the study was limited due to a high mortality rate in the treated and control groups, and since only the control and the high-dose groups were examined histopathologically.

The LOAEL was 126 mg/kg bw/d.

Two experiments were conducted to investigate the effects of feeding theophylline to Osborn-Mendel and Holtzmann rats at a dietary level of 0.5% (ca. 230 mg/kg bw/d). No induction of testicular atrophy, oligospermatogenesis and aspermatogenesis was observed after 14 weeks. However it was observed after 75 weeks in Osborn-Mendel rats and after 19 weeks in Holtzmann rats (Friedman at al. 1979, Weinberger, et. al. 1979). Because of the small group size (only 6-7 rats of 20 survived), the high mortality (up to 71%) and the single dose tested, the studies are regarded to be inappropriate for assessing the toxicological potential of the substance.
In contrast, no histopathological changes were found in testes in well documented subchronic studies in rats (see 3.1.4).

Conclusion:
Reproductive toxic effects (reduced litter number and pup viability, decreased live pup weight) were seen in a continuous breeding study in mice at doses, which caused also general toxicity. In 14 week-studies performed with rats and mice given theophylline by gavage or by feed, no significant differences in sperm

morphology and vaginal cytology parameters or histopathological effects in the sex organs were found between control and exposed animals (see 3.1.4).

3.1.7 Developmental Toxicity / Teratogenicity

Theophylline was evaluated for toxic and teratogenic effects in timed-pregnant Sprague-Dawley (CD) **rats** (NTIS 1985b, Lindstroem 1990). Theophylline (0, 1500, 3000, or 4000 ppm = 0, 124, 218, and 259 mg/kg bw/d) was administered continuously in the feed on gestational days (gd) 6 through 15.

During the treatment, dams exhibited clinical signs of toxicity consisting primarily of piloerection, transient weight loss, and rough coat. No dose related maternal deaths occurred during this investigation. Maternal body weight on gd 15, maternal weight gain during gestation (i.e. 19.5%, gd 0 through 20) and treatment (i.e. 53%, gd 6 through 15), and corrected maternal weight gain (i.e. 22.5%, maternal weight gain during gestation minus gravid uterine weight) decreased in a dose related manner and exhibited a significant difference among treatment groups with the high dose group significantly below controls.

During treatment and during the entire gestation period maternal food consumption decreased in a dose related manner and was significantly below controls in both the 3000 ppm and 4000 ppm dose groups during treatment, and in the 4000 ppm dose group for the entire gestation period. Maternal water consumption during treatment (g/day or g/kg/day) increased in a dose related manner up to 15% during gestation and up to 26% during treatment, with all theophylline treated groups significantly above controls.

There were no differences among treatment groups in the number of corpora lutea or implantation sites per dam, or in the percent preimplantation loss. Theophylline treatment had no effect on the percent of dead fetuses per litter, or on the percent of litters with one or more resorptions, dead fetuses, nonlive implants, or adversely affected implants, or on the percent of resorptions, dead fetuses, nonlive implants, or adversely affected implants per litter. Theophylline treatment resulted in a significant decrease in live fetuses per litter in the high dose group (12 and 13.8 in controls). Average fetal body weight per litter (male, female, and combined) decreased in a dose-related manner and was significant the mid (9%) and high dose (up to 15%).

Theophylline administered continuously from gd 6 to gd 15 had no effect on the percent of live fetuses malformed per litter or the percent of live male or female fetuses malformed per litter. Malformed fetuses per litter occurred with an incidence of 1.38%, 0.92%, 0.33%, and 1.57% for the vehicle control, low, medium, and high dose groups, respectively. The incidence of litters with one or more malformed live fetuses was unaffected by treatment. The incidence of litters with one or more external, skeletal, or visceral malformations was also unaffected by theophylline treatment.

Theophylline exposure resulted in significant dose-related fetotoxicity as evidenced by decreased average fetal body weight per litter at dose levels of 218, and 259 mg/kg bw/d and reduced number of live fetuses per litter at the high dose. These effects occurred in the presence of maternal toxicity (reduced corrected body weight gain 10% at 218 mg/kg bw/d, clinical signs like piloerection and rough coat), which was more pronounced at 259 mg/kg bw/d than at 218 mg/kg bw/d. (NTIS 1985b, Lindstroem 1990)

NOAEL maternal toxicity 1500 ppm (124 mg/kg bw/d)
NOAEL fetotoxicity 1500 ppm (124 mg/kg bw/d)
NOAEL teratogenicity 4000 ppm (259 mg/kg bw/d)

In an other study in which theophylline was administered in the drinking water to pregnant CD-1 **mice** (0, 750, 1500 or 2000 ppm = 282, 372, 396 mg/kg bw/d) on gd 6 through 15. Clear direct signs of maternal

toxicity occurred and were substantiated by distinct reductions in absolute and relative body weight gain (up to 31%) and reductions in water consumption in the mid - and high-dose group. Treatment at the 1500 ppm or 2000 ppm level resulted in an increase in the percent of resorptions (dead implants, 14, 27, 34%, respectively) and a decrease in the average fetal body weight (9 and 14%) per litter. The percentage of dead fetuses was not affected.
In the treated groups there was a slight, not statistically significant trend in the proportion of litters with malformed fetuses and for the incidence of external malformations in the mid and high-dose groups (cleft palates, exencephaly). Cleft palates also occurred in the control group, while exencephaly was only observed at the low and mid dose levels. However, it is well known from the literature (Schwetz et al. 1977, Beyer and Chernoff 1986) that particularly in this species, stress and depreviation of water during gestation may induce these types of malformations in the offsprings. Furthermore, this study was not designed to distinguish effects on the offspring caused by food and water deprivation from those caused by exposure to theophylline.
The authors, therefore, concluded that theophylline treatment was not associated with an increase in any particular malformation or group of malformations. (Lindström, 1990)

NOAEL maternal toxicity:	750 ppm (282 mg/kg bw/d)
NOAEL fetotoxicity:	750 ppm (282 mg/kg bw/d)
NOAEL teratogenicity:	2000 ppm (396 mg/kg bw/d)

A further study investigated the teratogenic and fetal toxicity of **i.v.** applications of theophylline and its relationship to maternal plasma levels in pregnant **rabbits**. Theophylline was administered i.v. to pregnant rabbits at doses of 15, 30 and 60 mg/kg bw/d using an automatic infusion pump from days 6-18 of gestation.
In the highest dose group a significant decrease in body weight was observed from gestation day 11 onwards, and a decrease in food intake was noted during days 7-23.
Theophylline showed clear signs of maternal toxicity at 60 mg/kg bw/d like accelerated respiration, abortion, sluggish startle reactions, dilatation of the auricular vessels and polyuria. There were no signs of maternal toxicity in the dams given 15 and 30 mg/kg bw/d.
Fetuses from the group treated with 60 mg/kg bw/d exhibited developmental toxicity. Developmental toxicity was substantiated by an increased number of late deaths, increased fetal body weights (about 10% below concurrent controls) and effects on fetal morphology. There was an increased rate of fetuses with cleft palates (8 out of 103 fetuses, in 2 of 14 litters) and with a 13th rib (63 out of 103 fetuses, number of affected litters not exactly specified). Whereas the cleft palate has to be considered as a malformation, the additional rib element is assessed as a variation because it appears quite frequently in control rabbit fetuses in the strain used for this study. No substance induced signs of developmental toxicology were observed in fetuses from the 15 and 30 mg/kg bw/d group. In the 15, 30 and 60 mg/kg bw/d groups, maternal plasma concentrations (C_{max}) during the treatment period were approximately 30, 56 and 106 µg/ml, respectively. These concentrations clearly exceed the effective therapeutic range of theophylline in clinical use (Shibata et al. 2000).

NOAEL maternal toxicity:	30 mg/kg bw/d
NOAEL fetotoxicity/teratogenicity:	30 mg/kg bw/d

Reproductive effects in humans

No association with congenital abnormalities was seen in studies with female theophylline drug users (Nelson and Forfar 1971) and women receiving theophylline during pregnancy did not deliver stillborn infants compared to controls (Neff and Leviton 1990).
No effects on development of premature infants were seen (Nelson et al., 1980, Ment et al. 1985). Theophylline therapy in surviving preterm children of birth weight <1501 g showed at 14 years of age significantly higher rate of cerebral palsy compared to children not exposed. In contrast children who had received theophylline achieved higher psychological test scores. There was no association between theophylline therapy and growth (Davis et al. 2000).

Conclusion:
Theophylline was not shown to be teratogenic in CD-1 mice at oral doses up to 396 mg/kg bw/d or in CD-1 rats at oral doses up to 259 mg/kg bw/d.
Intravenous theophylline was fetotoxic and teratogenic in rabbits at maternal toxic doses exceeding the effective therapeutic range (60 mg/kg bw/d i.v.).
At an oral dose of 218 and 396 mg/kg, fetotoxicity was observed in rats and mice, respectively, in the presence of maternal toxicity.
In humans, no association with congenital abnormalities or stillbirth were seen in studies with females receiving theophylline. Theophylline had no effects on the development of premature infants.

3.1.8 Carcinogenicity

In a 2-year bioassay, the substance was administered in corn oil by gavage to Fischer 344 rats and B6C3F1 mice (50 animals/sex). The rats were given 0, 7.5, 25, and 75 mg/kg bw/d (males and females); male mice received 0, 15, 50, and 150 mg/kg bw/d; female mice received 0, 7.5, 25, and 75 mg/kg bw/d.
In **rats**, mortality was similar in all groups. Body weights were reduced in all dosed groups. No increase in the incidence of neoplasms was observed. Increased incidence of periarteritis was found in high-dose males. This observed periarteritis may be a rat-specific response to vasodilators (see section 3.1.4).
In **mice**, mortality was increased in high-dose males. Body weights were reduced in high-dose males and females and in mid-dose females. No significantly increased incidences of neoplasms or non-neoplastic lesions were observed.
There was no evidence of carcinogenic activity of the substance in both, rats or mice (NTP 1998).

No data in humans on the carcinogenicity of theophylline per se are available.
Case-control studies did not show an association between total methylxanthine intake and breast cancer (Lubin et al. 1985b, Schairer et al. 1987, Rohan and McMichael 1988).

Conclusion:
Theophylline showed no carcinogenic activity in rats and mice up to the highest dose tested (75 mg/kg bw/d in rats and female mice and up to 150 mg/kg bw/d in male mice). In humans, case-control studies did not show an association between total methylxanthine intake and breast cancer

3.1.9 Pharmacological effects

Theophylline has the following major pharmacological actions: stimulation for cardiac muscle and CNS, relaxation of smooth muscle, especially bronchial muscle, vasodilator and act on the kidney as a diuretic.

Proposed mechanisms of xanthine-induced physiologic and pharmacological effects have included inhibition of phosphodiesterases, thereby increasing intracellular cyclic AMP, direct effects on intracellular calcium

concentration, indirect effects on intracellular calcium concentrations via cell membrane hyperpolarization, uncoupling of intracellular calcium increases with muscle contractile elements, and antagonism of adenosine receptors. A large body of evidence suggests that adenosine receptor antagonism is the most important factor responsible for most pharmacological effects of methylxanthines in doses that are administered therapeutically or consumed in xanthine-containing beverages.

Some of the adverse effects associated with theophylline appear to be mediated by inhibition of Phosphodiesterase III (e.g., hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (e.g., alterations in cerebral blood flow).

Theophylline increases the force of contraction of diaphragmatic muscles. This action appears to be due to enhancement of calcium uptake through an adenosine-mediated channel.

Toxic effects:

Mild toxicity includes headache, gastrointestinal disturbances, hypotension, irritability and insomnia. Severe symptoms include tachycardia, arrhythmia, cardiac arrest and serious neurological symptoms. Seizures and death have also occurred. Toxicity may be developed at serum levels of 20-30 µg/ml, whereas at levels below 15 µg/ml generally no symptoms were observed. In general, plasma concentrations correlate poorly with the ingested dose, and are dependent on factors like age, co-medication, bioavailability and smoking habits (Labovitz and Spector 1982, Helliwell and Berry 1979, Winek et al 1980, Woo et al 1980, Greenberg et al. 1984, Singer and Kolischenko 1985, Stavric 1988, Parr et al. 1990, Powell et al. 1993).

The accepted therapeutic serum concentration of theophylline ranges from 10-20 µg/ml, although improvement in forced respiratory volume in 1 s (FEV1), vital capacity and airways resistance have been demonstrated at plasma concentrations as low as 4-5 µg/ml (Minton and Henry 1996). The lower therapeutic level is taken as the NOAEL in humans.

Case-control studies did not show an association between total methylxanthine intake and benign breast disease (Lubin et al. 1985a, Rohan et al. 1989).

4. Hazards to the environment

4.1. Aquatic effects

The following acute toxicity tests with aquatic organisms are available:

Leuciscus idus	LC50(96h) = ca. 100 mg/l	BASF AG 1988b*
Daphnia magna	EC50(48h) = 178 mg/l	BASF AG 1989a
Scenedesmus subspicatus	ErC50 (72h) > 100 mg/l	BASF AG 2001b
(*Desmodesmus subspicatus*)	ErC10 (72h) > 100 mg/l	
	EbC50 (72h) > 100 mg/l	
	EbC10 (72 h) = 18.4 mg/l	
	NOEC (72 h) = 12.5 mg/l	

* At 100 mg/l 5 of 10 fish were dead after 96 h. At the next lower concentration of 46.4 mg/l no mortality occurs while at the next higher concentration of 215 mg/l all fish were dead.

In addition, also effect values for microorganisms are available:

Pseudomonas putida	EC50(17h) = 2110 mg/l	BASF AG 1988c
Activated sludge	EC20(3h) = 900 mg/l	BASF AG 2000b

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 98.1 and 101.3 % of the nominal values and the results were related to nominal concentrations.

Based on this data, Theophylline is not considered as hazardous to aquatic organisms.

Results from prolonged or chronic studies are not available.

Based on the most sensitive data, *Leuciscus idus* LC50(96h) 100 mg/l, a PNEC aqua of 0.1 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 theophylline on rice seedlings was investigated over a 6 day period. 2.5 mM theophylline (295 mg) reduced the root length by 67 % and shoot length by about 20 %. (Smyth 1992). As the tests were performed without soil but with filter paper the results cannot be used for the derivation of a PNECsoil.

5. Conclusions and Recommendations

5.1 Conclusions

1999 the estimated world production of theophylline amounts to 1,000 – 5,000 tons, the same level accounting for Germany and Europe.
Theophylline is a substance with wide disperse use. It is predominantly used as an antiasthmatic drug in the pharma sector (99%). 1% is used in cosmetic applications.

Production sites for the technical product: EU (Germany) 1, NAFTA 1, India 1 and China 5.

Furthermore theophylline is a naturally occurring substance in plants e.g. in black tea (200 – 400 mg/kg dry weight), coffee (appr. 5 mg/kg in green coffee beans) and cocoa (trace amounts) and therefore is a component in the respective beverages. The use in pharmaceutical applications and also the use in foods will be the predominant way of human exposure and of exposure of the environment.

Exposure of workers to theophylline during production is adequately controlled in the industry of the sponsored country.
Workplace measurements Germany : 0.1- ca. 0.5 mg/m^3 (8h)

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

Distribution modelling using Mackay, Level I, indicates that the main target compartment will be water with 99.98% (BASF AG 2000a).

Theophylline is indirectly photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 20 hours. According to OECD criteria the substance is readily biodegradable. The calculated hydrolysis rate is extremely slow ($T_{1/2}$ >1 year).
The log Kow of –0.0076 does not indicate a potential for bio - or geoaccumulation.
Short-term tests are available for fish, daphnia and algae. Based on acute toxicity studies theophylline is not considered as hazardous to aquatic organisms. Following the EU risk assessment procedure the PNEC aqua can be calculated to 0.1 mg/l by applying an assessment factor of 1000 on the most sensitive species (*Leuciscus idus* LC50(96h) 100 mg/l).

Theophylline is moderately toxic after oral uptake and of low toxicity after dermal and inhalative uptake.
LD50, rat (oral): 272 mg/kg bw , LC50, rat (inhalation, aerosol): >6.7 mg/l/4h, LD50, rat (dermal): >2000 mg/kg bw. Main symptoms following exposure are convulsion and accelerated respiration (oral) and irregular and accelerated respiration (inhalation).

The undiluted substance was not irritating to the eyes, the substance in a 50% aqueous dilution was not irritating to the skin of rabbits.

In repeated dose studies, theophylline was given to rats and mice by feed or by gavage. In rats theophylline caused nephropathy in all fed male rats and a dose-dependent periarteritis in all treated groups. Those effects are discussed to be secondary effects, due to the pharmacological properties (vasodilatation/ -

constriction) of methylxanthines. No histo-pathological changes were found in other organs including sex organs of rats and mice.
LOAEL: 75 mg/kg bw/d (rat, feed), 37.5 mg/kg bw/d (rat, gavage), LOAEL: 175 mg/kg bw/d (mouse, male, feed), 225 mg/kg bw/d (mouse, female, feed), NOAEL: 75 mg/kg bw/d (mouse male, gavage), 150 mg/kg bw/d (mouse female, gavage)

Theophylline was not mutagenic or clastogenic in most of the standard in vitro tests. Positive results were found only at high, cytotoxic concentrations and without metabolic activations.
Theophylline had no mutagenic or clastogenic effects in vivo.

In fertility/developmental toxicity studies in mice, the oral administration of theophylline resulted in changes in parental body weight and significant reproductive effects to the offspring (reduced mean number of litters, fewer live pups per litter, decreased live pup weight). No effects were observed in sperm morphology or in the estrous cycle in rats and mice in 14 week studies. LOAEL: 126 mg/kg bw/d.

Theophylline was not shown to be teratogenic in CD-1 mice at oral doses up to 396 mg/kg bw/d or in CD-1 rats at oral doses up to 259 mg/kg bw/d. At an oral dose of 218 and 396 mg/kg bw/d, fetotoxicity was observed in rats and mice, respectively, in the presence of maternal toxicity. Intravenous theophylline was fetotoxic and teratogenic in rabbits at maternal toxic doses exceeding the effective therapeutic range (60 mg/kg bw/d i.v.).
NOAEL rat maternal/fetotoxicity: 124 mg/kg bw/d, NOAEL rat teratogenicity: 259 mg/kg bw/d
NOAEL mouse maternal/fetotoxicity: 282 mg/kg bw/d, NOAEL mouse teratogenicity: 396 mg/kg bw/d
NOAEL rabbit maternal/fetotoxicity/teratogenicity: 30 mg/kg bw/d

Theophylline showed no carcinogenic activity in rats and mice when tested up to the highest doses (75 mg/kg bw/d rats, female mice and 150 mg/kg bw/d male mice).

In rats theophylline is rapidly and completely absorbed from the digestive tract and distributed to all organs except adipose tissue. It readily crosses the placenta and no blood-brain barrier was observed. Plasma half-life is between 1.2-4 hours in rats and 6-11.5 hours in dogs and strongly dependent on protein binding and dose. Theophylline is metabolized in the liver, mainly by the microsomal system. The metabolites are excreted into the bile and eliminated with the urine.
In humans theophylline is readily absorbed after oral intake and distributed in the different body tissues and breast milk. Theophylline is metabolized in the liver and excreted by the kidney. Only 7-12 % is excreted unchanged in the urine. Major metabolites are 1,3-dimethyluric acid (35-55 %), 1-methyluric acid (13-26 %) and 3-methylxanthine (9-18 %). The elimination half-time is 3-11 hours in adults.
Signs of intoxication are: headache, gastrointestinal disturbances, hypotension, irritability and insomnia, tachycardia, arrhythmia, cardiac arrest and serious neurological symptoms. Seizures and death have also occurred. Toxicity may be developed at serum levels of 20-30 µg/ml, whereas at levels below 15 µg/ml generally no symptoms were observed.
Case-control studies did not show an association between total methylxanthine intake and benign breast disease or breast cancer.
No association with congenital abnormalities or stillbirth were seen in studies with females receiving theophylline.
In premature infants no effect of theophylline on the development was seen.

5.2 Recommendations

The substance is currently of low priority of further work. However there is a recommendation for sharing the information on possible aggregated exposure with regulatory agencies responsible for food, pharmaceuticals and cosmetics

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Appendix 1

Date of last literature search: June 05, 2001 (update search for Human Health Endpoints in TOXLINE and MEDLINE; period covered: 1998 to May 2001)

Searched Toxicology Databases (January 11, 2000)
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

Searched Ecotoxicity / Environment Databases (Date of Search: January 11, 2000)
AQUASCI
BIOSIS
EMBASE
ESBIOBASE.
LIFESCI
OCEAN
POLLUAB
SCISEARCH
TOXCENTER
TOXLINE
ULIDATE
DATALOG
CHEMFATE
BIODEG
AQUIRE

HSDB

I U C L I D D a t a S e t

Existing Chemical ID: 58-55-9
CAS No. 58-55-9
EINECS Name theophylline
EC No. 200-385-7
Molecular Formula C7H8N4O2

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: 10-MAR-2003
Revision date:
Date of last Update: **10-MAR-2003**

Number of Pages: **127**

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
07-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: Theophylline
Mol. Formula: C7 H8 N4 O2
Mol. Weight: 180,16 g/mol

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

1.1.1 General Substance Information

Substance type: organic
Physical status: solid
Purity: 97 - 100 % w/w

Remark: USP grade with the specification to contain 97.0 - 102.0% active ingredient calculated on a dried basis, 0.5% max. weight loss on drying for the anhydrous form and 7.5 - 9.5% for the monohydrate form
Flag: Critical study for SIDS endpoint
27-JUL-2001 (1)

Substance type: organic
Physical status: solid
Colour: white
Odour: odourless

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

1.1.2 Spectra

1.2 Synonyms and Tradenames

1,3-Dimethylxanthine

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

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

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

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

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

Theophyllin, wasserfrei

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

1.3 Impurities

Remark: According to USP specification 0.15% max. residue on ignition
Flag: Critical study for SIDS endpoint
27-JUL-2001 (1)

1.4 Additives

1.5 Total Quantity

Remark: Consumption World Market (1999): 1.000-5.000 t/a
EU-Part: 1.000-5.000 t/a
BRD-Part: 1.000-5.000 t/a
Trend: weakly decreasing
Flag: Critical study for SIDS endpoint
27-JUL-2001

1.6.1 Labelling

Labelling: provisionally by manufacturer/importer
Symbols: (Xn) harmful
Specific limits: no
R-Phrases: (22) Harmful if swallowed
S-Phrases: (22) Do not breathe dust
(37/39) Wear suitable gloves and eye/face protection

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-2001 (2)

1.6.2 Classification

Classified: provisionally by manufacturer/importer
Class of danger: harmful
R-Phrases: (22) Harmful if swallowed

Flag: non confidential, Critical study for SIDS endpoint
07-MAR-2001 (2)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Wide dispersive use

Flag: non confidential, Critical study for SIDS endpoint
27-JUL-2001 (3)

Type: use
Category: Cosmetics

Remark: Additives: Substances which are added to cosmetic products, often in relatively small amounts, to impart or improve desirable properties or suppress (or minimize) undesirable properties.
Source: EU. Commission Decision 96/335/EC establishing an inventory and a common nomenclature of ingredients employed in cosmetic products. O.J. (L 132) 1, 1 Jun 1996.
Flag: non confidential, Critical study for SIDS endpoint
23-JAN-2003 (4)

Type: use
Category: Cosmetics

Remark: Treatment of cellulitis, skin aging
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
26-OCT-2000

Type: use
Category: Pharmaceuticals

Remark: Treatment of asthma
Source: Knoll AG Ludwigshafen
Flag: non confidential, Critical study for SIDS endpoint
29-JAN-2001 (5) (3)

Remark: Shares on the world market (1999):
Pharma: 99%
Cosmetics: 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 available

Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (6)

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
20-JUL-2001 (2)

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. 200-385-7

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

Type: ENCS
Additional Info: ENCS No. 9-847X

Remark: For ENCS chemical class or category name, refer to ENCS No. 9-847
ENCS CLASSIFICATION:
Low Molecular Heterocyclic Organic Compounds.
ENCS DESIGNATION:
Japanese Pharmacopoeia (8th Ed.) substance.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (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

Remark: Hazardous decomposition products: unknown
Flag: non confidential, Critical study for SIDS endpoint
12-FEB-2003 (2)

1.9.2 Components

1.10 Source of Exposure

Remark: Theophyllin can be prepared from dimethylurea and ethyl cyanoacetate and occurs naturally in black tea, green coffee beans, cacao cotyledon and dried mate in small and varying amounts.
The use in pharmaceutical applications and also the use in foods and beverages will be the predominant way of human exposure and of exposure of the environment.
Flag: non confidential, Critical study for SIDS endpoint
27-JUL-2001 (3)

1.11 Additional Remarks

Memo: hazardous reactions: flammable gases/vapours > 330°C

Flag: non confidential, Critical study for SIDS endpoint
12-FEB-2003 (2)

1.12 Last Literature Search

Type of Search: Internal and External
Chapters covered: 5.10
Date of Search: 06-OCT-2001

07-FEB-2003

1.13 Reviews

2.1 Melting Point

Value: 270 - 274 degree C

Reliability: (2) valid with restrictions
Reference book
Flag: Critical study for SIDS endpoint
20-JUL-2001 (2) (8)

Value: 272 degree C
Decomposition: yes at degree C

Remark: Decomposition temperature > 273°C
Test condition: According to DIN
03-NOV-2000 (5)

2.2 Boiling Point

Value:

Result: not relevant because of physical decomposition
Reliability: (2) valid with restrictions
expert judgement
Flag: Critical study for SIDS endpoint
20-JUL-2001

2.3 Density

Type: bulk density
Value: = 500 kg/m3 at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
20-JUL-2001 (5)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .000000007 hPa at 25 degree C

Method: other (calculated): MPBPWIN, Version 1.28

Result: VP = 5.12E-9 mmHg (Modified Grain Method)
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
20-JUL-2001 (9)

2.5 Partition Coefficient

log Pow: = -.008 at 23 degree C

Method: other (measured): according to OECD-guidelines of commission 67/548/EWG
GLP: no

Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
Flag: Critical study for SIDS endpoint
29-MAY-2002 (10)

log Pow: = -.028

Method: other (measured)

Remark: log Pow = -0.062 (calculated in accordance with the Hansch and Leo fragment method)
Test substance: theophylline, no further data
27-OCT-2000 (11)

log Pow: = -.02

Method: other (measured)

Method: Shake-flask method
03-NOV-2000 (12)

2.6.1 Solubility in different media

Solubility in: Water
Value: = .0055 vol% at 19.9 degree C

GLP: no

Method: saturated solution evaporated in "Rotavapor"
Remark: Temperature Solubility

°C	kg/kg (solution)
-0.1	0.0023
10.0	0.0034
19.9	0.0055
29.9	0.0083
39.5	0.0121
50.2	0.0189
60.0	0.0309
69.8	0.0573
80.2	0.0940
90.0	0.1196

Reliability: (2) valid with restrictions
Acceptable, well documented publicatio/study report which meets basic scientific principles
Flag: Critical study for SIDS endpoint
29-MAY-2002 (13)

Solubility in: Water

Value: = 8.3 g/l at 20 degree C
pH **value:** 4 - 6
Conc.: 20 g/l at 20 degree C

Descr.: of low solubility

Method: other

Reliability: (2) valid with restrictions
Reference book
Flag: Critical study for SIDS endpoint
29-MAY-2002 (2) (8)

Solubility in: Water
Value: = 7.4 g/l at 25 degree C

29-MAY-2002 (14)

Solubility in: Water
Value: = 8 g/l at 20 degree C
pH value: = 5
Conc.: 8 g/l at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
29-MAY-2002 (5)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

Remark: hardly flammable; ignition temperature > 610°C
Reliability: (4) not assignable
Manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
20-JUL-2001 (2)

2.10 Explosive Properties

Result: not explosive

Remark: not explosive according to the German blasting agent law (Sprengstoffgesetz)
Reliability: (4) not assignable
Manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
20-JUL-2001 (2)

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Remark: Dust explosive property class ST 1(German)
Flag: Critical study for SIDS endpoint
20-JUL-2001 (2)

Remark: Description: white, crystalline powder, odorless
Flag: Critical study for SIDS endpoint
20-JUL-2001 (2) (5) (3)

Remark: Vapors flammable > 330°C
Flag: Critical study for SIDS endpoint
20-JUL-2001 (2)

Remark: Solubilities:
ethanol: 12.5 g/l
chloroform: ca. 9 g/l
soluble: hot water, alkali hydroxides, ammonia and dilute hydrochloric acids
diethyl ether: sparingly soluble
Flag: Critical study for SIDS endpoint
27-OCT-2000 (8)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: = .0000000000192825 cm³/(molecule * sec)
Degradation: = 50 % after 20 hour(s)

Method: other (calculated): AOP, Version 1.87

Method: The computer program AOP is based on SAR methods developed by Atkinson.
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
28-JAN-2003 (15) (16)

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)

Remark: It is suggested that the compound may absorb sunlight and undergo phototransformation in water (according to Lyman et al., 1982) but no data are available to estimate photolytic half-life; the rate constant for the reaction with hydroxyl radicals in water is 6.3x10+9/M-sec (according to Buxton et al., 1988); assuming the concentration of hydroxyl radicals in eutrophic water to be 3x10-17 M (according to Mill and Mabey, 1985) the half-life in water has been estimated to be 42 days; it is assumed that the compound may biodegrade in natural water; based on the estimated Henry's law constant (Hine and Mookerjee, 1975) the volatilization from water should not be important; the estimated log Koc of 1.37 (according to Lyman et al., 1982) indicates that adsorption to suspended solid and sediment in water should be unimportant; the estimated bioconcentration factor of 0.6 (according to Lyman et al., 1982) suggests that bioconcentration in aquatic organisms may be not important
Reliability: (2) valid with restrictions

31-OCT-2000 (17) (18) (19) (20) (21) (22)

3.1.3 Stability in Soil

Remark: Based on the readily biodegradability in a screening test with sewage (Richardson and Bowron, 1985) it may be biodegradable in soil; the estimated log Koc of 1.37

(according to Lyman et al, 1982) indicates that it may be highly mobile in soil (according to Swann et al, 1983)

Reliability: (2) valid with restrictions
27-OCT-2000 (19) (21) (22)

3.2.1 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: surface water

Remark: River water, no further information
Result: Theophylline was detected at µg/l level by means of field desorption mass spectrometry, peak matching and comparison with mass spectrum of authentic standard; no further information given
27-OCT-2000 (23)

Type of measurement: background concentration
Medium: other

Result: Theophylline in the order of magnitude of 1 µg/l was detected in river water
Test condition: HPLC analysis
27-OCT-2000 (21)

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

Test substance: estimated log KOC = -0.2319
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
28-JAN-2003 (15)

Type: volatility
Method: other

Method: calculated with HENRYWIN, Version 3.00
Result: HENRYs LAW CONSTANT:
H = 1.7E-7 Pa*m3/mole at 25 °C
(H = 1.68E-12 atm*m3/mole)
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
20-JUL-2001 (15)

Type: volatility
Method: other: calculated with Mackay level I: Version 2.1

Result: H= 1.52E-08 Pa*m3/mole at 20 degree Celsius
Calculation basis:
water solubility: 8300 g/m3

Vp: 7.00E-7
log Kow -0.01

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

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
Environmental modelling centre, Trent University - 1999
Result: water: 99.98 %
air: 0.000000534 %
soil: 0.0078 %
sediment: 0.0079 %

Calculation basis:
water solubility: 8300 g/m3
Vp: 7.00E-7
log Kow -0.01
T: 20 °C
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
28-JAN-2003 (15) (24)

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: as prescribed by 1.1 - 1.4

Result: > 90 % degradation at the end of the 10-days-window
lag-Phase: 4 days,
degradation phase: 10 days,
Test condition: reference substande: aniline
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
28-JAN-2003 (25)

Result: readily biodegradable

Test condition: Methods for testing were those recommended by the Department of Environment, Standing Committee of Analysts (1981) and by King (1981), no further information available

31-OCT-2000 (21)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Result: Using the log Pow of -0.02 (according to Hansch and Leo, 1979) and a recommended regression equitation (according to Lyman et al., 1982) the bioconcentration factor has been estimated to be 0.6; consequently, bioaccumulation in aquatic organisms should not be important (Peer reviewed).

27-OCT-2000 (12) (19)

3.8 Additional Remarks

Remark: Environmental fate/exposure summary:
Release into the environment is expected during production and discharge of effluents from hospitals; it is suggested that theophylline may absorb sunlight and may photodegrade but rate is unknown; the compound may be biodegradable in water and soil (based on biodegradation screening test); adsorption to suspended solids and sediments in water and soil should be unimportant; volatilization from water shouldnot occur; the estimated bioconcentration factor indicates that this should be unimportant in aquatic organisms; if present in the atmosphere in the vapor phase, the reaction with photochemically produced hydroxyl radicalsmay be important (estimated half-life: 2.5 h) [Peer reviewed]

Reliability: (4) not assignable
secondary quotation

19-APR-2001 (26)

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: = 46.4
LC0: = 46.4
LC50: ca. 100
LC100: = 215

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

Remark: LC50 (1 h) >1000 mg/l
LC50 (4 h) >460, <1000 mg/l
LC50 (24 h) >220, <460 mg/l
LC50 (48 h) >100, <220 mg/l
LC50 (72 h, 96 h) ca. 100 mg/l
LC0 (48 h) = 50 mg/l

Groups of 10 fish were exposed to the test substance at nominal concentrations of 46.4, 100.0, 215.0, 464.0, and 1000.0 mg/l (pH was ca. 8.0, temperature was 19-20 degree C). No deaths were observed at the lowest test concentration and at 1 hour at all concentration levels. Deaths were observed at concentrations of 100 mg/l and more and occurred at 4 to 96 hours. The highest concentration was lethal to all fish within 4 h. At the end of the study (96 h), 5/10 fish exposed to 100 mg/l and all fish exposed to 215 mg/l and more had died.
Test substance: theophylline (anhydrous powder); according to the authors, purity was 99.5-100.5%
Reliability: (1) valid without restriction
test procedure according to national standard (DIN)
Flag: Critical study for SIDS endpoint
28-JAN-2003 (27)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 125
EC50: = 178
EC100: = 500

Method: other: Directive 79/831/EEC, C2 Annex V
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: EC50(48h) original value:178.48 mgl

concentrations (mg/l)	no. of mobile daphnids
0	20
3.9	20
7.8	20
16	20
31	20
63	20
125	18
250	2
500	0

Test condition: Data related to nominal concentrations.
test volume: 10 ml,
4 parallels and 1 uninoculated parallel,
concentration range: 39.06 - 5000 mg/l
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
28-JAN-2003 (28)

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: = 12.5
LOEC: = 25
EC10: = 18.4
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

Remark: The test substance was tested in the concentration range between 100 and 3,13 mg/l.
The dilution factor was 2.
Results are related to the nominal concentrations of the test item. The analytical recoveries varied between 98,1% and 101,3% at test initiation and between 98,8% and 100,2% at test termination.
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
28-JAN-2003 (29)

Species: Scenedesmus subspicatus (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** yes

NOEC: = 12.5
LOEC: = 25
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

Remark: The test substance was tested in the concentration range between 100 and 3,13 mg/l.
The dilution factor was 2.
Results are related to the nominal concentrations of the test item. The analytical recoveries varied between 98,1% and 101,3% at test initiation and between 98,8% and 100,2% at test termination.
Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint
28-JAN-2003 (30)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge
Exposure period: 180 minute(s)
Unit: mg/l **Analytical monitoring:**
EC50: > 1000
EC80 : > 1000
EC20 : ca. 900

Method: OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Test condition: inoculum concentration of dry substance: 1 g/l, concentration range: 100 - 1000 mg/l
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
28-JAN-2003 (31)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 1390
EC50: = 2110
EC90 : = 4140

Method: other: Growth inhibition test according to Bringmann and Kühn (DIN 38412, part 8, draft June 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: 39.06 - 5000 mg/l

Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions

Flag: Critical study for SIDS endpoint

28-JAN-2003 (32)

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
GLP: no data
Test substance: no data

Remark: The effect of theophylline on early development of rice seedlings (growth of roots and shoots) was examined after treatment over 5 or 6 days. The choosen concentration of 2.5mM reduced growth of root length of about 67% and that of shoots of about 20%
Reliability: (2) valid with restrictions
Acceptable, well documented publication/study report which meets basic scientific principles
Flag: Critical study for SIDS endpoint
28-JAN-2003 (33)

Species: other terrestrial plant

Result: Theophylline inhibits growth in seedlings of Coffea arabica (Coffee).
Reliability: (4) not assignable
secondary quotation
20-JUL-2001 (34)

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex: male/female
No. of Animals: 20
Vehicle: other: 0.5% Traganth in distilled water
Value: 272 mg/kg bw

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

Remark: LD50 (24 h; 14 d) = 273 (193 - 389) mg/kg (males)
LD50 (24 h; 14 d) = 272 (194 - 385) mg/kg (females)

Groups of 10 Sprague-Dawley rats/sex were administered the test substance at dose levels of 0, 100, 215, 261, 316, 464, and 1000 mg/kg and were observed for 14 days. No deaths were observed in controls and at 100 mg/kg; 3/20, 9/20, 14/20, 20/20, and 20/20 rats administered 215, 261, 316, 464, and 2000 mg/kg, respectively, died. All these deaths occurred within 24 hours after dosing. No clinical signs were observed at 100 mg/kg, fist clinical signs as increase in respiratory frequency at 215 mg/kg. Clinical signs included convulsions, accelerated respiration, eyelid closure, and salivation were observed at 1000 mg/kg between 1 and 6 hours.
Gross pathology: in some animals anemia was observed at 464 mg/kg. Several dead animals exhibited nonspecific bleeding in the thymus at doses between 316 and 1000 mg/kg.
Test substance: theophylline
Reliability: (1) valid without restriction
basic data given; comparable to guideline study
Flag: Critical study for SIDS endpoint
12-DEC-2001 (35)

Type: LD50
Species: rat
Value: = 225 mg/kg bw

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

Remark: no further data
Test substance: theophylline
Reliability: (4) not assignable
20-NOV-2001 (36)

Type: LD50

Species: mouse
Value: = 332 mg/kg bw

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

Remark: no further data
Test substance: theophylline
Reliability: (4) not assignable
20-NOV-2001 (3)

Type: LD50
Species: mouse
Value: = 235 mg/kg bw

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

Remark: no further data
Test substance: theophylline
Reliability: (4) not assignable
20-NOV-2001 (37)

Type: LD50
Species: mouse
Value: = 600 mg/kg bw

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

Remark: no further data
Test substance: theophylline
Reliability: (4) not assignable
20-NOV-2001 (38)

Type: LD50
Species: rabbit
Value: = 350 mg/kg bw

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

Remark: no further data
Test substance: theophylline
Reliability: (4) not assignable
20-NOV-2001 (39)

Type: LD50
Species: guinea pig
Value: = 183 mg/kg bw

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

Remark: no further data
Test substance: theophylline
Reliability: (4) not assignable
20-NOV-2001 (36)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Sex: male/female
No. of Animals: 10
Vehicle: other: Aerosil
Exposure time: 4 hour(s)
Value: > 6.7 mg/l

Method: OECD Guide-line 403 "Acute Inhalation Toxicity"
Year: 1989
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Groups of 5 Wistar rats/sex were exposed to a dust aerosol of the test substance using a head-nose inhalation system. The test substance was mixed with Aerosil (1 and 2 wt%) for generation of the inhalation atmosphere; analytical concentrations of the test substance amounted 2.39 and 6.7 mg/l. After exposure for 4 hours, all animals were observed for 14 days.
No deaths occurred. Clinical signs of toxicity included changes in respiration (irregular, accelerated, intermittent, gasping), eyelid closure (over the whole observation time), salivation, restlessness (over the whole observation time), and attempts to escape (up to 1/4h) were observed in both test concentrations.
Test substance: theophylline (anhydrous, micronized); according to the authors, purity was 99.5-100.5%
Reliability: (1) valid without restriction
guideline study (OECD)
Flag: Critical study for SIDS endpoint
12-DEC-2001 (40)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Sex: male/female
No. of Animals: 10
Vehicle: other: olive oil
Value: > 2000 mg/kg bw

Method: other: no data
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: No deaths and no substance related effects were observed in 5 male and 5 female Wistar rats after a semiocclusive application (24 h) of the test substance in olive oil

followed by a 14-day observation period. The application sites were washed after removal of the application patches.
Test substance: theophylline (anhydrous, micronized)
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
12-DEC-2001 (41)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Route of admin.: i.p.
Value: = 206 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (3)

Type: LD50
Species: rat
Route of admin.: i.p.
Value: = 188 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (42)

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 217 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (3)

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 70 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (43)

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

Method: other: no data
GLP: no

Test substance: other TS

Test substance: theophylline
05-SEP-2000 (44)

Type: LD50
Species: mouse
Route of admin.: s.c.
Value: = 138 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (45)

Type: LD50
Species: mouse
Route of admin.: s.c.
Value: = 184 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (46)

Type: LD50
Species: mouse
Route of admin.: i.m.
Value: = 271 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (47)

Type: LD50
Species: mouse
Route of admin.: i.v.
Value: = 136 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (48)

Type: LD50
Species: mouse
Route of admin.: i.v.
Value: = 210 mg/kg bw

Method: other: no data

GLP: no
Test substance: other TS

Test substance: theophylline
05-SEP-2000 (49)

Type: LD50
Species: rabbit
Route of admin.: i.v.
Value: = 150 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (47)

Type: LD50
Species: rat
Route of admin.: other: unspecified
Value: = 300 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (36)

Type: LD50
Species: mouse
Route of admin.: other: unspecified
Value: = 400 mg/kg bw

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

Test substance: theophylline
05-SEP-2000 (36)

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: One male and two female White Vienna rabbits were applied ca. 0.5 g of a 50% aqueous suspension of the test substance under semiocclusive conditions. After 4 h, the application patches were removed, and the application sites were washed. Scoring was made at 4, 24, 48, and 72 hours after beginning of the study. Very slight reddening was observed in the 2 females at 4 hours. No other signs of irritation were noted. Mean irritation index was 0.0.
Reliability: (1) valid without restriction guideline study (OECD)
Flag: Critical study for SIDS endpoint
12-DEC-2001 (50)

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. 51 mg) of the solid test substance was placed into the right conjunctival sac of each of 3 male White Vienna rabbits. The eyes were not rinsed. Scoring was made at 1, 24, 48, and 72 hours and at 8 days after instillation. Very slight corneal opacity was observed in 1-2 rabbits up to day 8. Slight to well-defined conjunctival redness and conjunctival swellings were observed in all 3 rabbits up to 72h and 48h, respectively. The findings were reversible in 2 of the 3 animals. On day 8 one animal showed conjuctiva redness (grad 2) and slight cornea opacity (grad 1) and keratitis. The effects could possible be due to mechanical irritation by the crystalline test substance. The iris was unaffected in each animal at each time. Mean irritation indices were 0.6 (corneal opacity), 0.0 (iritis), 1.8 (conjunctival redness), and 0.6 (conjunctival swelling).
Reliability: (2) valid with restrictions guideline study (OECD)
Flag: Critical study for SIDS endpoint
11-DEC-2001 (50)

5.3 Sensitization

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male/female
Strain: Fischer 344

Route of administration: oral feed
Exposure period: 14 weeks

Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: ca. 75, 125, 250 mg/kg bw/d (males); ca. 75, 125, 275 mg/kg bw/d (females) (1000, 2000, 4000 ppm in the diet)
Control Group: yes, concurrent no treatment
LOAEL: 75 mg/kg bw

Method: other: National Toxicology Program (NTP)
GLP: no data
Test substance: other TS

Remark: Theophylline is a non-specific phosphodiesterase inhibitor which may cause excessive vasodilatation. The mesenteric and pancreatic arteries in rats are particularly sensitive to the excessive vasodilator-pharmacological activity of theophylline, caffeine and other vasodilator drugs. The periarteritis may be a consequence of hemodynamic changes induced in the vascular wall. (Nyska et al.,1998)

Result: The effects of subchronic feeding of the test substance was investigated. Three groups of 10 Fischer 344/N rats/sex were fed diets containing the test substance at concentrations of 1000, 2000, and 4000 ppm. According to the authors, these concentrations corresponded to approximate daily doses of 75, 125, and 250 mg/kg bw/d, respectively, for males and 75, 125,and 275 mg/kg bw/d, respectively, for females. Control rats were fed unsupplemented diets.
There were no mortality or significant weight-gain depression in any of the treated groups. The food consumption was unaffected. There were no clinical findings attributed to theophylline exposure.
No substance-related signs of toxicity or gross lesions were observed. Mean cell volume and mean cell hemoglobin was significantly increased in both mid and high dose males. Segmented neutrophil counts were significantly increased in all dosed females. Absolute and relative kidney weights of the high dose males were significantly elevated. A treatment-related increase in the severity of nephropathy was observed in all males including the control group. However the severity of lesions progressed with dose (control and low dose: minimal, mid-dose: mild, high-dose: moderate).
A significant dose-dependent increase of the incidence of periarteritis of the medium-sized mesenteric arteries adjacent to the pancreas and/or mesenteric lymph nodes was found in the mid and high dose of males (2 and 3 animals resp.) and in all dose groups of females (1,1,5 animals). Periateritis was characterized by infiltration of mononuclear and polymorphonuclear leukocytes into the media and adventitia, and the more severe lesions included degeneration of medial smooth muscle and periarterial fibrosis. Increases in segmented neutrophiles counts were 1.18 (controls), 1.99; 1.72; 2.45 10e3/uL. These effects were also observed in the 2-year study in males of the highest dose group (75 mg/kg bw/d).
There were no significant differences between control and exposed rats in sperm morphology or vaginal cytology parameters. No histopathological findings were observed in

the sex organs.

The LOAEL of 75 mg/kg bw/d relates to periarteritis (females) and nephropathy (males).
Test condition: Groups of 10 animals/sex.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (51) (52) (53) (54)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: 4 weeks
Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: ca. 440 mg/kg bw/d, reduced to 220 mg/kg bw/d (8000 ppm in the diet, reduced to 4000 ppm after 2 weeks)
Control Group: yes, concurrent no treatment

Method: other
Year: 1991
GLP: yes
Test substance: other TS

Remark: only one dose tested
Result: Groups of 15 rats/sex were fed a diet containing the test substance at a concentration of 0 (control) or 8000 ppm. The concentration of the test substance was reduced to 4000 ppm starting in study week 3. No deaths occurred. Body weights of the treated rats were significantly lower than control. Food consumption was reduced throughout the study in treated males and during the initial 2 weeks in treated females. Tail lesions (sores) and red encrustations around the nose were seen in the treated group. Individual treated males exhibited paraphimosis. Hematological parameters were unaffected. Clinical chemistry and urinalysis revealed some changes; however, according to the authors, these alterations were considered to be representative of a pharmacologic effect of the test substance and not indicative of systemic toxicity. At necropsy, significantly reduced weights of heart and kidneys were seen in males. No treatment-related changes were seen, except the tail sores mentioned above.
Test substance: theophylline; according to the authors, purity was 100% (analyzed)
Reliability: (2) valid with restrictions
10-MAR-2003 (55)

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: oral feed
Exposure period: 16 days
Frequency of treatment: continuously in the diet
Post exposure period: no
Doses: 50, 100, 250, 450, 1000 mg/kg bw/d (males), 75, 150, 250, 450, 1100 mg/kg/d (females) (500, 1000, 2000, 4000, 8000 ppm)

Control Group: yes

Method: other: National Toxicology Program (NTP)
Year: 1998
GLP: no data
Test substance: other TS

Result: All rats survived until the end of the study. No clinical findings were attribute to theophylline treatment. The final mean body weights and body weight gains of 8000 ppm males and females were significantly less than those of the controls. The absolute and relative testes weights of 4000 ppm males were significantly greater than those of the controls. Increase incidences of uterine hypoplasia were observed microscopically in exposed groups of females.
Test condition: 5 males and 5 females
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
basic data given, not enough animals per group
10-MAR-2003 (56) (53)

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: gavage
Exposure period: 14 weeks
Frequency of treatment: 5 d/w
Post exposure period: none
Doses: 37.5, 75, 150 mg/kg bw/d
Control Group: yes, concurrent vehicle
LOAEL: 37.5 mg/kg bw

Method: other: National Toxicology Program (NTP)
GLP: no data
Test substance: other TS

Remark: Theophylline is a non-specific phosphodiesterase inhibitor which may cause excessive vasodilatation. The mesenteric and pancreatic arteries in rats are particularly sensitive to the excessive vasodilator-pharmacological activity of theophylline, caffeine and other vasodilator drugs. The periarteritis may be a consequence of hemodynamic changes induced in the vascular wall. (Nyska et al.,1998)
Result: The effects of subchronic exposure to the test substance was investigated. Three groups of 10 Fischer 344/N rats/sex were administered the test substance in corn oil; control rats were given the vehicle. One male and one female of the high dose group died; however, this was not statistically significant. Mean body weight gain was significantly increased in high dose females. No substance-related signs of toxicity or gross lesions were observed. Mean cell volume of high dose males and mean cell hemoglobin of all treated males was significantly increased.
A dose-dependent increase in incidences of mesenteric and/or pancreatic periarteritis was observed in all treated males (control: 1/10; 37.5 mg/kg 1/10; 75 mg/kg: 2/10; 150 mg/kg: 5/10) and females (0/10; 2/10; 2/10; 3/10 resp.). The periarteritis observed in one control males was more consistent with that commonly observed in aged rats and consisted of minimal, focal lymphocytes accumulation

adjacent to the artery. Periateritis was characterized by infiltration of mononuclear and polymorphonuclear leukocytes into the media and adventitia, and the more severe lesions included degeneration of medial smooth muscle and periarterial fibrosis. Theophylline-related arterial lesions were noted in the 2 year study only in male rats given the high dose of 75 mg/kg bw, this effect was statistically significant.
There were no significant differences between control and exposed rats in sperm morphology or vaginal cytology parameters. No histological changes were seen in the sex organs.
The LOAEL of 37.5 mg/kg bw/d relates to periarteritis in both sexes.

Test condition: Groups of 10 animals/sex.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (51) (52) (53) (54)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 4 weeks
Frequency of treatment: daily
Post exposure period: none
Doses: 200 mg/kg bw/d
Control Group: yes, concurrent vehicle

Method: other: no data
Year: 1991
GLP: yes
Test substance: other TS

Remark: only one dose tested
Result: Groups of 15 rats/sex were administered a suspension of the test substance in corn oil at a dose level of 200 mg/kg/d or the vehicle only (control). Four treated males died. Body weights of the treated females were significantly higher than control. Food consumption was enhanced throughout the study in treated females. Tail lesions (sores) and red encrustations around the nose were seen in the treated group. Individual treated males exhibited chromodacryorrhea, dyspnea, and transient salivation. Hematological parameters were unaffected. Clinical chemistry and urinalysis revealed some changes; however, according to the authors, these alterations were considered to be representative of a pharmacologic effect of the test substance and not indicative of systemic toxicity. At necropsy, significantly increased weights of liver, kidneys and heart were seen in dosed females. Tail sores were seen in the treated rats. Darkend lungs, splenic pallor, and fluid-filled stomachs were observed in several animals receiving the test substance. No other treatment-related changes were seen.
Test substance: theophylline; according to the authors, purity was 100% (analyzed)
Reliability: (2) valid with restrictions

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: gavage
Exposure period: 16 days
Frequency of treatment: once and twice daily
Post exposure period: no
Doses: 12.5 (twice daily), 25 (once daily), 50 (once daily), 50 (twice daily), 100 (once daily), 200 (once daily), 200 (twice daily), 400 (once daily) mg/kg bw
Control Group: yes

Method: other: National Toxicology Program (NTP)
Year: 1998
GLP: no data
Test substance: other TS

Result: All rats receiving 400 mg/kg once daily and all but one female receiving 200 mg/kg twice daily died during the study. In groups dosed once daily, final mean body weight gains of males receiving 100 or 200 mg/kg and mean body weight gains of females receiving 50, 100, or 200 mg/kg were less than those of the controls. The final main body weights and body weight gains of groups receiving theophylline twice daily were generally similar to those of groups receiving the same daily dosage once daily. Clinical findings included rapid or labored respiration, hunched posture, and squinting. In groups dosed once daily, absolute and relative uterus weights of females receiving 100 or 200 mg/kg once daily were significantly less than those of the controls, and absolute and relative uterus weights of females receiving 100 mg/kg once daily were significantly less than those of females receiving 50 mg/kg twice daily. Uterine atrophy was observed in three females receiving 200 mg/kg twice daily. Periarteritis of the mesenteric arteries was observed in two males and two females receiving 400 mg/kg once daily.
Test condition: 5 males and 5 females/group
Test substance: theophylline in corn oil; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
basic data given, not enough animals per group
Flag: Critical study for SIDS endpoint
10-MAR-2003 (56) (53)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: oral feed
Exposure period: 14 weeks
Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: ca. 175, 400, 800 mg/kg bw/d (males); ca. 225, 425, 850 mg/kg bw/d (females) (1000, 2000, 4000 ppm in the diet)
Control Group: yes, concurrent no treatment
LOAEL: 1000 ppm

Method: other: National Toxicology Program (NTP)
Year: 1998

GLP: no data
Test substance: other TS

Result: The effects of subchronic feeding to the test substance was investigated. Three groups of 10 mice/sex were fed diets containing the test substance at concentrations of 1000, 2000, and 4000 ppm. According to the authors, these concentrations corresponded to approximate daily doses of 175, 400, and 800 mg/kg, respectively, for males and 225, 425, and 850 mg/kg, respectively, for females. Control mice were fed unsupplemented diets. No deaths occurred throughout the study. The final mean body weights and body weight gains of all treated mice were significantly decreased. Food consumption was unaffected. There were no clinical findings related to theophylline exposure.
Leukocyte and segmented neutrophil counts were significantly increased in high dose males and females and in mid dose females; lymphocyte counts were significantly increased in high dose males.
Histopathology revealed a hepathocyte glycogen depletion, which is considered as a result of lower body weights. No other findings.
There were no biological significant differences between control and exposed mice in sperm morphology or vaginal cytology parameters. No histological changes were observed in the sex organs. The LOAEL based on the reduced body weight in males and females.
LOAEL 1000 ppm (175 mg/kg/d, males), (225 mg/kg/d, females)
Test condition: Groups of 10 animals/sex.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (51) (52) (53)

Species: mouse **Sex:** male/female
Strain: Swiss
Route of administration: oral feed
Exposure period: 23 days
Frequency of treatment: continuously in the diet
Post exposure period: none
Doses: ca. 1600 mg/kg bw/d, reduced to 800 mg/kg bw/d (8000 ppm in the diet, reduced to 4000 ppm after 2 weeks)
Control Group: yes, concurrent no treatment

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

Remark: only one dose tested
Result: Groups of 15 mice/sex were fed a diet containing the test substance at a concentration of 0 (control) or 8000 ppm; treatment period was planned to be 4 weeks. The concentration of the test substance was reduced to 4000 ppm starting in study week 3; treatment was stopped on day 23. One treated mouse died. Body weight gains were decreased in treated males and increased in treated females. Food consumption was increased in females during weeks 3 and 4 (administration of the reduced dose). Hunched posture, tremors, and hypoactivity were seen in several treated

males. Hematological parameters were unaffected. Clinical chemistry revealed significantly decreased creatinine levels for treated females and increased potassium level for

treated males and females. At necropsy, significantly reduced testicular weights (absolute and relative) were seen in males. No clear treatment-related gross observations were noted.
Test substance: theophylline; according to the authors, purity was 100% (analyzed)
Reliability: (2) valid with restrictions
10-MAR-2003 (57)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: oral feed
Exposure period: 16 days
Frequency of treatment: continuously in the diet
Post exposure period: no
Doses: 250, 475, 950, 1800 2000 mg/kg bw/d (males; 300, 450, 1225, 2000 4375 mg/kg bw (females) (500, 1000, 2000, 4000, 8000 ppm)
Control Group: yes

Method: other: National Toxicology Program (NTP)
Year: 1998
GLP: no data
Test substance: other TS

Result: All mice survived until the end of the study. Final mean body weights of 4000 and 8000 ppm females and main body weihgt gains of 2000, 4000 and 8000 ppm females were significantly greater than those of the controls. Feed consumptionby exposed groups was similar to that by the controls, except that by the 8000 ppm males, which was approximately 40% the amount of feed consumed by the control group. Histopathologic examinations were not performed due to the absence of mortality and significant exposure-related lesions.
Test condition: 5 males and 5 females/group
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
10-MAR-2003 (53)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 14 weeks
Frequency of treatment: no data
Post exposure period: none
Doses: 75, 150, 300 mg/kg bw/d
Control Group: yes, concurrent vehicle

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

Result: The effects of subchronic exposure to the test substance was investigated. Three groups of 10 mice/sex were administered the test substance in corn oil; control mice were given the vehicle. Three males and all females of the high dose group,

one low dose male and one control female died. Final mean body weights and body weight gains were significantly reduced in both mid and high dose males. There were no clinical findings attributed to theophylline treatment. Mean cell volume and mean cell hemoglobine of high dose males was significantly increased. Histopathology revealed no findings attributed to the test substance or changes in the sex organs.
Histopathology revealed a hepathocyte glycogen depletion in the females, which is considered as a result of lower body weights. Lymphoid depletion (minimal to moderate) was observed in the thymus and spleen of the high-dose male and as considered to be related to stress associated with theophylline administration.
There were no biological significant differences between control and exposed mice in sperm morphology or vaginal cytology parameters. The NOAEL based on the reduced bodyweight in males and females.
NOAEL male; 75 mg/kg bw/d; female 150 mg/kg bw/d

Test condition: Groups of 10 animals/sex.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (51) (52) (53)

Species: mouse **Sex:** male/female
Strain: Swiss
Route of administration: gavage
Exposure period: 4 weeks
Frequency of treatment: daily
Post exposure period: none
Doses: 200 mg/kg bw/d
Control Group: yes, concurrent vehicle

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

Remark: only one dose tested
Result: Groups of 15 mice/sex were administered a suspension of the test substance in corn oil at a dose level of 200 mg/kg/d or the vehicle only (control) for 4 weeks. Twelve males and 6 females of the treated group died. Body weight gains and organ weights were similar to control. Food consumption was increased in females throughout the study. Treated animals experienced squinting, hypoactivity, dyspnea, abrasions on the neck, and alopecia. Prior to death, ataxia, rapid respiration, and hyperactivity followed by hypoactivity, and in males, and apparent distention of the scrotal sac was noted. Hematological and clinical-chemical parameters were unaffected. Gross necropsy revealed alopecia and scabs on the neck in the dosed group.
Test substance: theophylline; according to the authors, purity was 100% (analyzed)
Reliability: (3) invalid
only one dose tested
10-MAR-2003 (57)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 16 days

Frequency of treatment: once and twice daily
Post exposure period: no
Doses: 12.5 (twice daily), 25 (once daily), 50 (once daily), 50 (twice daily), 100 (once daily), 200 (once daily), 200 (twice daily), 400 (once daily) mg/kg bw
Control Group: yes

Method: other: National Toxicology Program (NTP)
Year: 1998
GLP: no data
Test substance: other TS

Result: Three males and all females receiving 400 mg/kg once daily died on day 1. There were no significant differences in final mean body weights or body weight gains. There were no histopathologic findings attrbuted directly to theophylline.
Test condition: 5 males and 5 females/group
Test substance: theophylline in corn oil; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
16-JUL-2001 (53)

5.5 Genetic Toxicity 'in Vitro'

Type: Cytogenetic assay
System of testing: Chinese hamster cell line (CHL)
Concentration: 250, 500, 1000, 2000 ug/ml
Metabolic activation: with and without
Result: ambiguous

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

Remark: Chromosomal aberration test with and without metabolic activation with S-9 mix prepared from rat liver homgenate. CHL cells were exposed for 24 or 48 h to concentrations of 0.25, 0.5, and 1.0 without S-9 and to 0.5, 1.0, and 2.0 mg/ml with S-9. Preparations were made by an air-dry method, 100 metaphases were evaluated. Chromosomal aberrations were observed in the absence of S-9 in the 500 and 1000 ug/ml dose, but not in the presence of S-9.
The number of polyploid cells was not significantly altered. Negative results were given after short (4 hours, no exact data) exposure with and without S9 mix up to 2000 ug/ml. This study is evaluated as negative by NTP
Test substance: theophylline

Reliability: (3) invalid
not well documented, data lacking
12-DEC-2001 (58) (59)

Type: Cytogenetic assay
System of testing: Human lymphocytes
Concentration: 0, 100, 150, 200 ug/ml

Metabolic activation: no data
Result: positive

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

Test substance: commercial tablets (Theobid 300, Cipla Ltd. Bombay)
Reliability: (4) not assignable
secondary literature
12-DEC-2001 (60)

Type: other
System of testing: Euglena gracilis
Concentration: 480 ug/ml
Metabolic activation: no data
Result: positive

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

Remark: Induction of auxotrophic mutations was observed at a concentration 12 mg/25 ml.
unsuitable test system
Test substance: theophylline
Reliability: (3) invalid
19-NOV-2001 (61) (62)

Type: Bacillus subtilis recombination assay
System of testing: Bacillus subtilis
Concentration: no data
Metabolic activation: with and without
Result: negative

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

Remark: essential details lacking, sec. literature
Test substance: theophylline
Reliability: (3) invalid
20-NOV-2001 (63)

Type: other
System of testing: Silkworm
Concentration: no data
Metabolic activation: without
Result: negative

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

Remark: Test for mutations.
unsuitable test system
Test substance: theophylline

Reliability: (3) invalid
19-NOV-2001 (63)

Type: Sister chromatid exchange assay
System of testing: Hamster lung fibroblasts

Concentration: no data
Metabolic activation: without
Result: positive

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

Test substance: theophylline
Reliability: (4) not assignable
secondary literature
12-DEC-2001 (63)

Type: Cytogenetic assay
System of testing: Hamster lung fibroblasts
Concentration: no data
Metabolic activation: without
Result: positive

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

Remark: Chromosomal aberration test.
Test substance: theophylline
Reliability: (4) not assignable
secondary literature
12-DEC-2001 (64) (65) (63) (66)

Type: Sister chromatid exchange assay
System of testing: Human embryo fibroblasts
Concentration: no data
Metabolic activation: without
Result: positive

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

Test substance: theophylline
Reliability: (4) not assignable
secondary literature
12-DEC-2001 (63)

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

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

Remark: essential details lacking

Test substance: theophylline
Reliability: (3) invalid

20-NOV-2001 (67)

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

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

Remark: essential details lacking, secondary literature
Test substance: theophylline
Reliability: (3) invalid
20-NOV-2001 (63) (68)

Type: Bacterial gene mutation assay
System of testing: Escherichia coli
Concentration: 150 ug/ml
Metabolic activation: without
Result: positive

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

Remark: essentail details lacking
Phage T5 resistance was increased, no mutagenicity screening.
Test substance: theophylline
Reliability: (3) invalid
20-NOV-2001 (69) (70)

Type: Bacterial gene mutation assay
System of testing: Escherichia coli 15h+m-
Concentration: no data
Metabolic activation: without
Result: positive

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

Remark: essentail details lacking
Methionine auxotrophy to methionine protrophy was induced. No strain for mutagenicity screening.
Test substance: theophylline
Reliability: (3) invalid
20-NOV-2001 (71)

Type: other: Bacillus subtilis multigene sporulation test
System of testing: Bacillus subtilis 168DB, BY886, hcr9 (exc-)
Concentration: 7.5, 10, 15, 20 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: Multigene sporulation test; the cultures were incubated with the test substance at 37 degree C for 60 minutes, plates were scored 48 hours later. The frequency of asporogenic colonies was increased, indicated by reduced pigmentation. unsuitable test system

Result: positive in very high concentrations at 15 mg/ml
Test substance: theophylline
Reliability: (3) invalid
19-NOV-2001 (72)

Type: HGPRT assay
System of testing: Chinese hamster lung V79 cells
Concentration: 5, 7, 9 ug/ml
Metabolic activation: with and without
Result: negative

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

Remark: 6- thioguanine-resistant
Test substance: theophylline
Reliability: (4) not assignable
secondary literature
12-DEC-2001 (68)

Type: Cytogenetic assay
System of testing: Allium cepa
Concentration: no data
Metabolic activation: without
Result: positive

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

Remark: Chromosomal aberration test.
Test substance: theophylline
Reliability: (3) invalid
19-NOV-2001 (73) (74) (75)

Type: Cytogenetic assay
System of testing: Vicia faba
Concentration: ca. 900, 3600 ug/ml (5, 20 mM)
Metabolic activation: without
Result: negative

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

Remark: Chromosomal aberration test without metabolic activation. The test substance did not induce chromosomal aberrations in the root tips of field beans (Vicia faba var. minor) after treatment with 20 mM for 1 hour at 15 degree C or after treatmant with 5 mM for 2 h at 20 degree C. Control cultures were treated with water; chromosomes were evaluated 3 hours after treatment.
However, the test substance (5 mM) enhanced the chromosomal aberrations induced by X-rays (30 R) 2.7-fold when given as post-treatment immediately after irradiation.
Test substance: theophylline
Reliability: (3) invalid
20-NOV-2001 (76)

Type: other
System of testing: Ophiostoma multiannulatum
Concentration: 0.6%
Metabolic activation: without
Result: positive

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

Remark: Auxotrophic mutation test in the ascomycetes. At a concentration of 0.6% theophyllin, 0.6% mutants were observed in isolated conidia (control: 0.06% mutants). unsuitable test system
Test substance: theophylline
Reliability: (3) invalid
19-NOV-2001 (77) (78)

Type: Sister chromatid exchange assay
System of testing: Chinese hamster Don-6 cells and human diploid fibroblasts
Concentration: no data
Metabolic activation: without
Result: positive

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

Test substance: theophylline
Reliability: (4) not assignable
secondary literature
12-DEC-2001 (79)

Type: other: micronucleus test
System of testing: Chinese hamster Don-6 cells and human diploid fibroblasts
Concentration: no data
Metabolic activation: without
Result: negative

Method: other: no data
GLP: no data

Test substance: other TS

Test substance: theophylline
Reliability: (4) not assignable
secondary literature
12-DEC-2001 (79)

Type: Cytogenetic assay
System of testing: HeLa cells
Concentration: ca. 13 mg/ml (1.3% solution)
Metabolic activation: without
Result: positive

Method: other: no data
Year: 1966
GLP: no
Test substance: other TS

Remark: Test on chromatid breaks metabolic activation. The cells were incubated with a 1.3% solution of the test substance for 1 hour and were fixed after 30 hours. In the treated cells, the incidence of chromatid breaks was 68/2776 chromosomes (2.4%) compared with 3/3208 chromosomes (0.1% in control cultures).
No unsuitable test system, relevant methodological deficiencies
Test substance: theophylline
Reliability: (3) invalid
the testconcentration was more than 10 mM, tumor cell line,
12-DEC-2001 (80)

Type: Cytogenetic assay
System of testing: Human lymphocytes
Concentration: ca. 18, 180, 1800 ug/ml (0.1, 1, 10 mM)
Metabolic activation: without
Result: negative

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

Remark: Test on antimitotic activity and chromosomal damage. Human lymphocytes were obtained from adult healthy donors and incubated with the test substance for 72 hours. One thousand cells from each culture were examined and the number of cells in mitosis (mitotic index) was recorded. Mitotic rate was 16% of control at the low concentration (antimitotic effect), while no mitosis was seen at the mid and high concentration (cytostatic effect). No chromosome damage was seen.
Result: chromosomal damage: negative
antimitotic/cytostatic activity: positive
Test substance: theophylline
Reliability: (3) invalid
Unsuitable test system
12-DEC-2001 (81)

Type: other
System of testing: Photobacterium leiognathi (dark variant)
Concentration: 20 - 2000 ug/ml
Metabolic activation: without
Result: positive

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

Remark: Bioluminescence assay; 2 mg/ml (2000 ug/ml) induced a rapid luminescence within 30 min; the minimal concentration that reacted positive in this assay was 20 ug/ml.
unsuitable test system
Test substance: theophylline
Reliability: (3) invalid
19-NOV-2001 (82)

Type: Cytogenetic assay
System of testing: Chinese hamster ovary (CHO) cells
Concentration: 510, 555, 600 ug/ml
Metabolic activation: with and without
Result: negative

Method: other: as reported by Galloway, S.M. et al.: Environ. Mol. Mutagen. 10 (suppl. 10), 1-175
Year: 1987
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 Aorclor 1254-pretreated male Sprague-Dawley rats; scoring of 100 cells/dose level; harvest time: 22 h (-S-9) and 12 h (+S-9). Vehicle controls (DMSO) and positive controls (mitomycin-C without S-9 and cylophosphamide with S-9) were included. No cytotoxicity was observed at the concentrations used.
Test substance: theophylline; according to the authors, purity was >99%

Reliability: (2) valid with restrictions
comparable to guideline study, key study for ICCA robust summary
Flag: Critical study for SIDS endpoint
19-NOV-2001 (53)

Type: Ames test
System of testing: Salmonella typhimurium TA97, TA98, TA100, TA1535
Concentration: 100, 333, 1000, 3333, 10000 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: as reported by Zeiger, E. et al.: Environ. Mol. Mutagen. 11 (suppl. 12), 1-158
Year: 1988
GLP: no data
Test substance: other TS

Remark: Reverse mutation 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. Negative (vehicle) controls and positive controls (2-aminoanthracene for all tester strains with S-9; sodium azide for TA100 and TA1535, 9-aminoacridine for TA97, 4-nitro-o-phenylenediamine for TA98 without S-9) were included. No cyctotoxic effect of the test substance was noted unter the conditions used.

Test substance: theophylline; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
comparable to guideline study
Flag: Critical study for SIDS endpoint
22-JAN-2001 (53) (83)

Type: Ames test
System of testing: Salmonella typhimurium TA97a, TA100, TA102, TA104
Concentration: 1 - 10000 ug/plate (see remark)
Metabolic activation: with and without
Result: negative

Method: other: according to Maron, D.M. and Ames, B.N.: Mutat. Res. 113, 173-215
Year: 1983
GLP: no data
Test substance: other TS

Remark: Plate incorporation test with and without metabolic activation with S-9 mix prepared from rat liver homogenate.
Test concentrations:
1, 10, 100, 1000, 5000, 10000 ug/plate (TA97a, TA100)
1, 5, 10, 50, 100, 500, 1000, 5000, 10000 ug/plate (TA102)
1, 5, 10, 50, 100, 500, 1000 ug/plate (TA104)
Very weak mutagenic activity (factor up to 1.5) was observed in tester strains TA104 and TA102 in the presence of S-9 (not dose dependend).
Cytotoxity was observed at 10000 ug/plate.
No second experiment for confirmation was done.
Test substance: theophylline
Reliability: (2) valid with restrictions
19-NOV-2001 (84)

Type: Sister chromatid exchange assay
System of testing: Chinese hamster ovary (CHO-K1-BH4) cells
Concentration: ca. 18, 90, 360 ug/ml (0.1, 0.5, 2.0 mM)
Metabolic activation: without
Result: positive

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

Remark: Sister chromatid exchange test without metabolic activation. The cells were incubated with the test substance (0.1 mM for 26 hours, or 0.5 and 2 mM for 46 hours). SCE per chromosome was determined from 15-25 second-division cells. The number

of SCEs was slightly (factor up to 2.8), but significantly increased; this effect showed a trend to dose-response. In addition, the test substance potentiated the toxic effects of methylnitrosurea and reduced cloning efficiency and cellular growth rate.
Only without S9 mix tested.

Test substance: theophylline

Reliability: (3) invalid
Only without S9 mix tested, combined study.

12-DEC-2001 (85)

Type: Cytogenetic assay
System of testing: human lymphocytes
Concentration: 1, 10, 100 ug/ml
Metabolic activation: without
Result: positive

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

Remark: Chromosomal aberrations were observed at concentrations of 10 and 100 ug/ml. No possible the evaluate the results. They authors used not the conventional criteria for a chromosomal evaluation.
Test substance: theophylline
Reliability: (3) invalid
20-NOV-2001 (86)

Type: Sister chromatid exchange assay
System of testing: human lymphocytes
Concentration: 1, 10, 100 ug/ml
Metabolic activation: without
Result: negative

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

Remark: Sister chromatid exchanges were observed at concentrations of 10 and 100 ug/ml (factor 1.2).
Test substance: theophylline
Reliability: (2) valid with restrictions
12-DEC-2001 (86)

Type: Cytogenetic assay
System of testing: FM3A cells
Concentration: ca. 577, 1135 ug/ml (3.2, 6.3 mM)
Metabolic activation: without
Result: positive

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

Remark: Chromosomal aberration test without metabolic activation in FM3A cells, a cell line established from the spontaneously developed mammary carcinoma of a C3H mouse. The test was carried out at a concentration with showed moderate (20-40%) and considerable (50-70%) growth inhibition, as determined in a preliminary cytotoxicity test. The cells were incubated with the test substance for 24 and 48 hours; 100 metaphase cells per preparation were scored for chromosome aberrations. According to the authors, substances producing chromosomal aberrations in more than 10% of the metaphases

were judged to be positive.

The low concentration produced 20% and 68% aberrant metaphases after 24 and 48 hours, respectively; the high concentration produced 46% and 56% aberrant metaphases after 24 and 48 hours, respectively. Chromosomal aberrations included chromatid gaps, isochromatid gaps, chromatid breaks, ring formation, exchanges, and fragmentation.
Unsuitable test system

Test substance: theophylline
Reliability: (3) invalid
20-NOV-2001 (87)

Type: Cytogenetic assay
System of testing: human lymphocytes
Concentration: 250, 500, 750 ug/ml
Metabolic activation: without
Result: positive

Method: other: according to Weinstein, D. et al.: Mutat. Res. 20, 441-443
Year: 1973
GLP: no
Test substance: other TS

Remark: Test on antimitotic activity and chromosomal damage. The test substance was added to the lymphocytes at the 48th hour of incubation, colcemid was added at the 72nd hour for 2 hours; thereafter, the cells were harvested. The experiment was conducted in triplicate. A total of 50 metaphases was analyzed per concentration for each experiment (total of 150 metaphases per concentration level). At the mid and high concentration level, mitotic index was significantly reduced and the incidence of chromosomal abnormalities was significantly elevated.
No data was available about the chromosomal evaluation (i.e. aberrations with and without gaps). The study presented the results only in a graphical manner. No data was given about the number of chromosomal breaks observed.

Test substance: theophylline
Reliability: (3) invalid
19-NOV-2001 (88)

Type: Mouse lymphoma assay
System of testing: L5178Y tk+/- cells
Concentration: up to 5 mg/ml
Metabolic activation: with and without
Result: negative

Method: other: according Clive, 1975 and japanes guideline
Year: 1999
GLP: yes
Test substance: other TS

Result: Neither clastogen nor aneugen effects were found in the first test. With longer treatment of 24h the authors found weakly positive results.
Test condition: Two different tests were performed. In the first was with an incubation time of 3 hours, the second with a 24 h

incubation time. The first experiment was carried out in duplicate cultures according to the UKEMS guidelines, but in the 24 h experiment single cultures were used.

Test substance: theophylline
Reliability: (2) valid with restrictions
comparable to guideline study
Flag: Critical study for SIDS endpoint

06-JUL-2001 (89) (90)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: rat **Sex:** male
Strain: Osborne-Mendel
Route of admin.: oral feed
Exposure period: 75 weeks
Doses: ca. 230 mg/kg bw/d (0.5% in the diet)
Result: negative

Method: other: according to Green, S. et al.: J. Pharmacol. Exp. Ther. 187, 437-443
Year: 1973
GLP: no data
Test substance: other TS

Remark: Chromosomal aberration test with spermatogonial cells of the testes of rats that had been administered the test substance at a dose level of 0.5% in the diet for 75 weeks (part of a fertility study; see also chapter 5.8). One thousand cells per animal were counted to determine the mitotic index and an entire slide was counted for chromosome breaks. No substance-related cytogenetic damage and no effect on mitotic activity was observed. Six treated and 5 untreated control rats were used.
Test substance: theophylline; according to the authors, purity was >95%
Reliability: (2) valid with restrictions
only one dose were used
Flag: Critical study for SIDS endpoint

10-MAR-2003 (91)

Type: Cytogenetic assay
Species: mouse **Sex:** male
Strain: B6C3F1
Route of admin.: i.p.
Exposure period: single dose
Doses: 62.5, 125, 250 mg/kg or 37.5, 75, 150 mg/kg
Result: negative

Method: other: according to McFee, A.F.: Environ. Mol. Mutagen. 13, 325-331
Year: 1989
GLP: no data
Test substance: other TS

Result: Five groups of 8 mice were injected with the test substance

at dose levels of 62.5 mg/kg (1/4 MTD), 125 mg/kg (1/2 MTD), and 250 mg/kg (MTD; a group of 7 mice); corn oil (the vehicle); or 200 mg/kg dimethylbenzanthracene (positive control) and were sacrificed 18 hours later. Another five

groups of 8 mice were injected with the test substance at dose levels of 37.5, 75, and 150 mg/kg; corn oil; or 25 mg/kg DMBA and were sacrificed 36 hours later. Bone marrow cells were prepared from the femur; 400 metaphases/mouse were scored for chromosome aberrations. The test substance did not significantly increase the incidence of chromosomal aberrations when compared with vehicle controls.
The % aberration per cell ranged from 2.0 (control) to 3.43 (250 mg/kg) at 18 h and 2.25 (control) to 3.5 (lowest dose, not dose-depending) at 36h.

Test substance: theophylline
Reliability: (2) valid with restrictions
comparable to guideline study

12-DEC-2001 (92) (53)

Type: Cytogenetic assay
Species: mouse **Sex:** male
Strain: B6C3F1
Route of admin.: i.p.
Exposure period: single dose
Doses: 62.5, 125, 250 mg/kg
Result: negative

Method: other: according to McFee, A.F.: Mut. Res. 264, 219-224, 1991
Year: 1991
GLP: no data
Test substance: other TS

Remark: Groups of 10 male mice were given a single i.p. injection of the test substance in corn oil; controls were administered dimethylbenzathracene (positive control) or the vehicle. The animals were sacrificed at 18 or 36 hours after injection. Bone marrow were prepared from the femur for evaluation 50 first-division metaphases for chromosomal aberrations. No toxicity was observed at the doses used.
Test condition: Groups of 10 male mice.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
omparable to guideline study
Flag: Critical study for SIDS endpoint

28-JAN-2003 (92) (53)

Type: Cytogenetic assay
Species: rat **Sex:** no data
Strain: no data
Route of admin.: unspecified
Exposure period: no data
Doses: no data
Result: negative

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

Remark: Bone marrow chromosomal aberration test.
Test substance: theophylline

Reliability: (4) not assignable
No further data, secondary literature

12-DEC-2001 (63) (66)

Type: Dominant lethal assay
Species: mouse **Sex:** male
Strain: Abyssinian
Route of admin.: i.p.
Exposure period: single dose
Doses: 380, 480 mg/kg
Result: negative

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

Remark: ICR/Ha Swiss mice were used, males were 8-10 weeks old and females 8-10 weeks old when mated.
Each male mouse was treated and subsequently caged with 3 untreated virgin female mise, which replaced weekly for 8 consecutive wk, in one experiment mating were restricted to 3 week.
Doses were 380 mg/kg 6 males; 480 mg/kg 7 and 8 males.
No detailed data about implantations etc. evaliable.
Test substance: theophylline
Reliability: (3) invalid

20-NOV-2001 (93) (94)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of admin.: oral feed
Exposure period: 14 weeks
Doses: ca. 175, 400, 800 mg/kg bw/d (males); ca. 225, 425, 850 mg/kg bw/d (females) (1000, 2000, 4000 ppm in the diet)
Result: negative

Method: other: as reported by MacGregor, J.T. et al.: Fundam. Appl. Toxicol. 14, 513-522
Year: 1990
GLP: no data
Test substance: other TS

Remark: Peripheral blood samples were collected from groups of 10 mice/sex at the end of a 14-week feeding study (see chapter 5.4). Smears were prepared immediately for evaluation of micronuclei, fixed in absolute methanol and stained with a spezific fluorescent dye mixture. Slides were scanned using a semi-automated image analysis system, to determine the frequency of nuclei in 10,000 normochromatic erythrocytes (NCE) from each 10 animal/dose. No increase of micronucleated cells were determined. A slight cytotoxic effect was observed based on the decrease in percent PCE.
Test condition: Groups of 5 animals/sex.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
comparable to guideline study
Flag: Critical study for SIDS endpoint

10-MAR-2003 (53) (95)

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of admin.: gavage
Exposure period: 14 weeks
Doses: 75, 150, 300 mg/kg bw/d (males); 75, 150 mg/kg bw/d (females)
Result: negative

Method: other: as reported by MacGregor, J.T. et al.: Fundam. Appl. Toxicol. 14, 513-522,1990
Year: 1990
GLP: no data
Test substance: other TS

Remark: Peripheral blood samples were collected from groups of 7-10 mice/sex at the end of a 14-week feeding study (see chapter 5.4). Smears were prepared immediately for evaluation of micronuclei, fixed in absolute methanol and stained with a spezific fluorescent dye mixture. Slides were scanned using a semi-automated image analysis system, to determine the frequency of nuclei in 10,000 normochromatic erythrocytes (NCE) from each animal/dose. No increase of micronucleated cells were determined. A slight cytotoxic effect was observed based on the decrease in percent PCE.
Test condition: 7-10 animals/group, no data about the number of males and females.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (2) valid with restrictions
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (53) (95)

Type: Sister chromatid exchange assay
Species: mouse **Sex:** male
Strain: Swiss
Route of admin.: i.p.
Exposure period: single dose
Doses: 0, 12.5, 25, 50 mg/kg
Result: negative

Method: other: according to McFee, A.F. et al.: Mutat. Res. 119, 83-88
Year: 1983
GLP: no data
Test substance: other TS

Method: Groups of 5 mice were administered the test substance (12.5, 25, or 50 mg/kg), DMSO (vehicle control), or 1.5 mg/kg of Mitomycin C (positive) control). Bromodeoxyuridine (BrdU) tablets had been implanted s.c. 1 h prior to dosing; colchicine was injected i.p. 22 h after BrdU implantation. The mice were sacrificed 24 h after BrdU implantation. Bone marrow smears were prepared for SCE analysis. Thirty s-division cells per animal (150 cells per dose level) were scored.
Remark: According to the authors, these results indicated that the test substance induced significant SCE in bone marrow cells of mice, but the factors are only 1.3; 1.4; and 1.6 in comparison

to the control.

Factor is described as the test substance induced SCEs/cell divided by SCEs/cell in the control group.
A factor between 1.8 - 2.0 indicates a slightly positive effect. A factor > 2.0 is a clearly positive effect.
This endpoint (SCEs) is not qualified for a key study, because the interpretation of the data is unclear.

Result: Mean number of SCE/cell was 5.4, 5.6, and 6.7 at the low, mid and high dose level, respectively, 4.1 in the vehicle control and 21.6 in the positive control.
Test substance: theophylline
Reliability: (2) valid with restrictions
10-MAR-2003 (84)

Type: Sister chromatid exchange assay
Species: mouse **Sex:** male
Strain: B6C3F1
Route of admin.: i.p.
Exposure period: single dose
Doses: 62.5, 125, 250 mg/kg
Result: negative

Method: other: according to McFee, A.F.: Environ. Mol. Mutagen. 13, 325-331
Year: 1989
GLP: no data
Test substance: other TS

Method: Groups of 4 mice were injected with the test substance at dose levels of 62.5 mg/kg (1/4 MTD), 125 mg/kg (1/2 MTD), and 250 mg/kg (MTD); corn oil (the vehicle); or 2.5 mg/kg dimethylbenzanthracene (positive control) and were sacrificed 24 hours later. Bone marrow cells were prepared from the femur; 50 first-division cells/mouse were scored for chromosome aberration, 25 second-division cells/mouse were scored for SCEs.
Remark: Factor is described as the test substance induced SCEs/cell divided SCEs/cells in the control group.
A factor between 1.8 - 2.0 indicates a slight positive effect. A factor > 2.0 is a clearly positive effect.
This endpoint (SCEs) is not qualified for a key study, because the interpretation of the data is unclear.
Result: The mean number of SCEs per cell was elevated above control values in the lowest dose group, amd increased further at higher doses. A modest increase in the number of SCEs was observed (factor 1.8) at the 250 mg/kg dose (in comparison to the control). Theophylline had no effect on rate of proliferation among marrow cells since the average generation time for cells from treated animals was not significantly different from controls.
Test substance: theophylline
Reliability: (2) valid with restrictions
05-FEB-2003 (92)

Type: Sister chromatid exchange assay
Species: Chinese hamster **Sex:** no data
Strain: no data
Route of admin.: gavage
Exposure period: single dose
Doses: 0, 30, 75, 150, 225, 300, 450, 600 mg/kg
Result: positive

Method: other: no data
Year: 1982
GLP: no data
Test substance: other TS

Remark: Tablet method (implantation of BrdU tablets). Elevated SCE levels were seen in bone marrow cells of treated animals. Results only in a graphical manner.
Test substance: theophylline
Reliability: (3) invalid
Documentation insufficient for assessment
12-DEC-2001 (96)

Type: other: host-mediated assay
Species: mouse **Sex:** no data
Strain: Swiss
Route of admin.: i.m.
Exposure period: single dose
Doses: up to 10000 ug/ml (ca. 300 mg/kg bw)
Result: negative

Method: other
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 theophylline. 1000 ug/0.1 ml was the highest concentration tested.
Test substance: theophylline
Reliability: (3) invalid
Documentation insufficient for assessment
12-DEC-2001 (97)

Type: other: host-mediated assay
Species: mouse **Sex:** no data
Strain: no data
Route of admin.: i.p.
Exposure period: single dose
Doses: no data
Result: negative

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

Remark: Gene mutation assay with in-vivo metabolic activation (i.p. injection to the mouse) with Salmonella typhimurium G46.
Test substance: theophylline

Reliability: (3) invalid
Documentation insufficient for assessment

12-DEC-2001 (73)

5.7 Carcinogenicity

Species: rat **Sex:** male/female
Strain: Fischer 344
Route of administration: gavage
Exposure period: 2 years
Frequency of treatment: 5 d/w
Post exposure period: none
Doses: 7.5, 25, 75 mg/kg bw/d
Result: negative
Control Group: yes, concurrent vehicle

Method: other: National Toxicology Program (NTP)
Year: 1998
GLP: no data
Test substance: other TS

Result: The carcinogenic activity of the test substance was investigated. Groups of 50 Fischer 344/N rats/sex were administered the test substance in corn oil at doses of 0 (control), 7.5, 25, and 75 mg/kg bw/d for 2 years. Mortality was similar in all groups. Final mean body weights of all dosed animals were significantly reduced. No significantly increased incidences of neoplasms were found in the treated rats. The incidence of chronic inflammation of the mesenteric arteries (periarteritis) was significantly increased in high dose males. There were dose-related negative trends in the incidence of mammary gland fibroadenoma and combined fibroadenoma or carcinoma in the females; according to the authors, these changes correlated with decreased body weights.
According to the authors, there was no evidence of carcinogenic activity in Fischer 344/N rats.

Test condition: Groups of 50 animals/sex.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (53) (54)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: gavage
Exposure period: 2 years
Frequency of treatment: 5 d/w
Post exposure period: none
Doses: 15, 50, 150 mg/kg bw/d (males); 7.5, 25, 75 mg/kg bw/d (females)
Result: negative
Control Group: yes, concurrent vehicle

Method: other: National Toxicology Program (NTP)
Year: 1998

GLP: no data
Test substance: other TS

Result: The carcinogenic activity of the test substance was investigated. Groups of 50 male mice were administered the test substance in corn oil at doses of 0 (control), 15, 50, and 150 mg/kg bw/d; groups of 50 female mice were administered 0, 7.5, 25, and 75 mg/kg bw/d. Mortality was significantly increased in high dose males. Final mean body weights of high dose males, high dose females, and mid dose females were significantly reduced. No significantly increased incidences of nonneoplastic lesions and neoplasms were found in the treated mice. Decreased incidences of hepatocellular adenomas and and hepatocellular adenomas or carcinomas (combined) was found in the treated mice. Male mice had a pattern of nonneoplastic liver lesions along with silver staining helical organisms in the liver consistent with Helicobacter hepaticus infection. The incidences of these liver lesions were significantly lowered in high dose males.
According to the authors, increases in the incidences of hepatocellular neoplasms in male mice had been shown to be associated with Helicobacter hepaticus infection when hepatitis was also present. Thus, interpretation of the decreased incidences of liver neoplasms was difficult. Incidences of lesions at other sites observed in this study were not considered to be significantly impacted by Helicobacter hepaticus infection or its associated hepatitis.
According to the authors, there was no evidence of carcinogenic activity in B6C3F1 mice.
Test condition: Groups of 50 animals/sex.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (53)

5.8.1 Toxicity to Fertility

Type: Fertility
Species: rat
Sex: male
Strain: Osborne-Mendel
Route of administration: oral feed
Exposure Period: 75 weeks
Frequency of treatment: continuously in the diet
Premating Exposure Period
male: no mating
Duration of test: 75 weeks
Doses: ca. 230 mg/kg bw/d (0.5% in the diet)
Control Group: yes, concurrent no treatment

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

Remark: Because the small group size (only 6-7 rats of 20 survived), the high mortality (up to 71%) and the single dose tested, the study is regarded to be of limited value for assessing the toxicological potential of the substance

Result: The effect of a high level of the test substance on the testes and spermatogensis was studied. Groups of 20 male Osborne-Mendel rats were fed a diet containing the test substance at a concentration of 0.5% (ca. 230 mg/kg/d) or unsupplemented diet (control group). Six rats per group were sacrificed after 14 weeks of treatment; survivors were sacrificed after 75 weeks. Blood samples were collected prior to each sacrifice for routine hematology and analysis of serum for urea nitrogen (BUN) and glucose concentration and for activities of glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), and alkaline phosphatase (AP). Gross necropsy and histopathological examination was performed. Survival was not significantly different among the groups; 6 control rats and 6 treated rats each were examined after both 14 and 75 weeks. The test substance had little effect on body weight gain until 20 weeks, at which time an impairment of growth became apparent. At 75 weeks, body weights of the surviving treated rats were moderately depressed when compared with control. Treated rats had significantly increased kidney, adrenal, and pituitary weights. Hematological and clinical-chemical parameters were unaffected.
After 14 weeks of feeding, none of the 6 dosed rats had testicular atrophy. At 75 weeks, the incidence of testicular atrophy and aspermatogenesis was increased. Two out of 6 surviving rats of the treated group had treatment-related testicular atrophy, one rat showed oligospermatogenesis and another, aspermatogenesis. No neoplastic or preneoplastic lesions were detected.
According to the authors, these results indicated that the test substance produced testicular atrophy, oligospermatogenesis and aspermatogenesis.

No chromosomal damage was detected in spermatogonial cells prepared from the testes of the rats used in this study (see chapter 5.6)

Test substance: theophylline; according to the authors, purity was >95%
Reliability: (3) invalid
10-MAR-2003 (91) (98)

Type: Fertility
Species: rat
Sex: male
Strain: other: Holtzman
Route of administration: oral feed
Exposure Period: 19 weeks
Frequency of treatment: continuously in the diet
Premating Exposure Period
male: no mating
Duration of test: 19 weeks
Doses: ca. 230 mg/kg bw/d (0.5% in the diet)
Control Group: yes, concurrent no treatment

Method: other: no data
Year: 1979
GLP: no data

Test substance: other TS

Remark: Because the small group size (only 6-7 rats of 20 survived), the high mortality (up to 71%) and the single dose tested, the study is regarded to be of limited value for assessing the toxicological potential of the substance

Result: The effect of a high level of the test substance on the testes and spermatogensis was studied. A group of 24 male Holtzman rats was fed a diet containing the test substance at a concentration of 0.5% (ca. 230 mg/kg/d); 35 rats were fed an unsupplemented diet (control group). Survivors were sacrificed after 19 weeks. Blood samples were collected prior to sacrifice for routine hematology and analysis of serum for urea nitrogen (BUN) and glucose concentration and for activities of glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), and alkaline phosphatase (AP). Necropsy was limited to the testes and accessory sexual organs.
Mortality was significantly increased in the treated group; 6 control rats and 17 treated rats died until termaination of feeding. Most of the deaths occurred during the first 5 weeks and appeared to be due to pulmonary disease. Body weight gain, food intake and food efficiency of the treated rats was significantly decreased. Serum testosterone was slightly decreased. Testicular atrophy, oligospermatogenesis, and aspermatogenesis was seen in 6/7, 5/7, and 1/7 treated rats, respectively. No testicular damage was found in the control rats. No arteritis was observed in the treated group.
According to the authors, these results indicated that the test substance produced testicular atrophy, oligospermatogenesis and aspermatogenesis.

Test substance: theophylline; according to the authors, purity was >95%

Reliability: (3) invalid

10-MAR-2003 (91) (98)

Type: Fertility
Species: mouse
Sex: male/female
Strain: CD-1
Route of administration: oral feed
Exposure Period: 18 weeks (Task 2)
Frequency of treatment: continuously in the diet
Premating Exposure Period
male: 1 week
female: 1 week
Doses: ca. 126, 260, 500 mg/kg bw/d (0.075, 0.15, 0.3 % in the diet)
Control Group: yes, concurrent no treatment

Method: other: continuos breeding (RACB)
Year: 1985
GLP: yes
Test substance: other TS

Result: The effects of the test substance on reproduction and fertility was studied in CD-1 mice according to the RACB protocol. During the Task 2 continuous cohabitation study, the mice were fed diets containing the test substance at

concentrations of 0.075, 0.15, and 0.5%. According to the authors, these concentrations corresponded to doses of ca. 126, 260, and 500 mg/kg bw/d, respectively. Dosed groups consisted of 20 mice/sex; control group consisted of 40 mice/sex. During Task 2, the animals were treated for a total of 18 weeks (1 week prior to cohabitation, 14 weeks of cohabitation, 3 weeks post cohabitation).

Three control and 4 low dose mice died. Alopecia was observed in all treated animals (20-25% of the low dose mice and >50% in both mid and high dose mice) and in one control mouse (less severe than observed in the dosed groups). According to the authors, this was considered to be a sign of general toxicity.

Severe reproductive effects were found. The mean number of litter/pair was reduced by 19% in the high dose group. The number of live pups/litter was significantly reduced in all dosed groups (reduction by 22%, 29%, and 42% at the low, mid and high dose level, respectively). Live pup weights adjusted for the litter size were significantly decreased in the high dose group (by 6%). The number of days to delivery was prolonged (3-5 days) in the high dose group.

After delivery and evaluation of the Task 3 litters, the females were evaluated for vaginal cyclicity for 7 days. Then, the F0 mice of the control and high dose group were necropsied. In the high dose females, terminal body weights and relative liver weights were increased (by 5% and 11%, respectively). The estrous cycle was unaffected. In high dose males, terminal body weights were decreased by 7% when compared with controls. Relative seminal vesicle weights were decreased by 19%. Epididymal sperm density was reduced by 20%. The percent motile and the percent of abnormal morphologic forms was not affected in high dose males.

No second generation analysis was performed.

According to the authors, administration of the test substance resulted in significant adverse reproductive effects (affected offsprings and changes of the male reproductive organs) in the absence of changes in parental body weights. The reproductive effects were not considered to be associated with the alopecia.

A NOEL was not achieved in this study.
LOAEL 126 mg/kg bw/d

Test condition: Task 2: 3 dosed groups (20 mice/sex/group); 1 control group (40 mice/sex).
Test substance: theophylline
Reliability: (2) valid with restrictions
very high doses, high mortality in controls
Flag: Critical study for SIDS endpoint
10-MAR-2003 (52) (99)

5.8.2 Developmental Toxicity/Teratogenicity

Species: mouse **Sex:** female

Strain:	CD-1
Route of administration:	drinking water
Exposure period:	days 6 to 15 of gestation
Frequency of treatment:	continuously in the drinking water
Duration of test:	until day 17 of gestation

Doses: ca. 282, 372, 396 mg/kg bw/d (0.075%, 0.15%, 0.20% in the drinking water)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxity: ca. 282 mg/kg bw
NOAEL Teratogenicity: ca. 396 mg/kg bw

Method: other: National Toxicology Program (NTP)
Year: 1990
GLP: yes
Test substance: other TS

Result: The developmental toxicity of the test substance was investigated in groups of 23-33 pregnant mice. The mice were administered the test substance in the drinking water at concentrations of 0% (control), 0.075%, 0.15%, 0.20%) on gestational days 6 to 15. According to the authors, estimated daily intake of the test substance was 0, 282, 372, and 396 mg/kg, respectively. At day 17 of gestation, the dams were sacrificed.

Maternal body weight gain during gestation and corrected weight gain was decreased in the mid and high dose group. Maternal body weight gain during treatment and gravid uterine weight was decreased in the high dose group. Water consumption was decreased at the mid and high dose level while food consumption was similar in all groups. The percentage resorptions/litter was increased in the mid and high dose group (dead implants 14, 27 and 34%). Average mean fetal weight (male and female) was significantly decreased (9 and 14%) in the mid and high dose group.
In the treated groups there was a slight, not statistically significant trend in the proportion of litters with malformed fetuses and for the incidence of external malformations in the mid and high-dose groups (cleft palates, exencephaly). Cleft palates also occurred in the control group, while exencephaly was only observed at the low and mid dose levels. However, it is well known from the literature (Schwetz et al. 1977, Beyer and Chernoff, 1986) that particularly in this species, stress and depreviation of water during gestation may induce these types of malformations in the offsprings. Furthermore, this study was not designed to distinguish effects on the offspring caused by food and water deprivation from those caused by exposure to theophylline.
The authors, therefore, concluded that theophylline treatment was not associated with an increase in any particular malformation or group of malformations.

The no observable adverse effect levels (NOAELs) were 282 mg/kg bw/d for maternal toxicity and fetotoxicity. NOAEL teratogenicity: 396 mg/kg bw/d.

Test condition: Groups of 23-33 pregnant mice.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (100) (101) (102)

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 bw/d
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 75 mg/kg bw
NOAEL Teratogenicity: = 320 mg/kg bw

Method: other: no data
Year: 1968
GLP: no
Test substance: other TS

Remark: Signs of embryo/fetotoxicity were observed at doses that were already maternally toxic (100 mg/kg/more). An increased incidence of resorptions was seen at doses of 130 mg/kg and more. No further information.
Test substance: theophylline
Reliability: (3) invalid
only abstract
10-MAR-2003 (103)

Species: mouse **Sex:** male/female
Strain: CD-1
Route of administration: gavage
Frequency of treatment: daily
Duration of test: 21 days
Doses: 20, 60, 200 mg/kg bw/d
Control Group: yes, concurrent vehicle

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

Remark: Short term reproductive and developmental toxicity screen. One group of male and two groups (A and B) of female mice per each dose group were used. Males were treated after mating (day 0) from day 3 to day 20. Group A females were treated from day 0 to day 20 and were sacrificed on day 21. Group B females were treated from gestation day 8 to day 14 and were allowed to deliver and litters were evaluated on postnatal days 0, 1 and 4.
Result: Theophylline affected none of the examined parameters of general, reproductive and developmental toxicity at any dose level.
Test substance: theophylline
Reliability: (3) invalid
The study is limited by the screening method
10-MAR-2003 (104)

Species: rat **Sex:** female
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: days 6 to 15 of gestation

Frequency of treatment: continuously in the diet
Duration of test: until day 20 of gestation

Doses: ca. 124, 218, 259 mg/kg bw/d (0.15, 0.30, 0.40% in the diet)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxity: 124 mg/kg bw
NOAEL Teratogenicity: 259 mg/kg bw

Method: other: National Toxicology Program (NTP)
Year: 1985
GLP: yes
Test substance: other TS

Result: The developmental toxicity of the test substance was investigated in groups of 20-21 pregnant rats. The rats were fed diets containing the test substance at concentrations of 0.15%, 0.30% and 0.40% on gestational days 6 to 15. According to the authors, estimated daily intake of the test substance was 124, 218, and 259 mg/kg, respectively. Control rats were fed unsupplemented diet. At day 20 of gestation, the dams were sacrificed.

Maternal body weight gain during gestation and treatment as well as corrected weight gain was decreased in the high dose group. Food consumption was decreased at the high dose level; water consumption was increased in all treated groups. Gravid uterine weights were decreased, showing a trend to dose-response. The number of live fetuses/litter was significantly decreased at the high dose level. Average mean fetal weight (male, female, and combined) was significantly decreased in the mid and high dose group. The incidence of malformed fetuses/litter was similar in all groups (1.4%, 0.9%, 0.3%, and 1.6% in the control, low, mid, and high dose group, respectively).

According to the authors, administration of the test substance to pregnant rats resulted in significant dose-related fetotoxicity. The no observable adverse effect levels (NOAELs) were 124 mg/kg bw/d for maternal toxicity and for developmental toxicity (fetotoxicity). NOAEL teratogenicity 259 mg/kg bw/d.
Test condition: Groups of 20-21 pregnant rats.
Test substance: theophylline; according to the authors, purity was >99%
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2003 (105) (100) (101) (102)

Species: rat **Sex:** female
Strain: no data
Route of administration: oral feed
Exposure period: days 15 to 20 of gestation
Frequency of treatment: continuously in the diet
Duration of test: no data
Doses: ca. 165, 249 mg/kg bw/d (0.4, 0.6% in the diet)
Control Group: no data specified

Method: other: no data
GLP: no

Test substance: other TS

Result: No significant increase in the incidence of resorptions or malformations was observed.
Test substance: theophylline
Reliability: (4) not assignable
secondary literature
10-MAR-2003 (106)

Species: mouse **Sex:** male/female
Strain: CD-1
Route of administration: oral feed
Frequency of treatment: continuously in the diet
Doses: ca. 126, 260, 500 mg/kg bw/d (0.075, 0.15, 0.30% in the diet)
Control Group: yes, concurrent no treatment

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

Remark: Method: NTP reproductive assessment by continuous breeding (RACB);
Task 1: dose range-finding for about two weeks
Task 2: continuous breeding for 14 weeks
Task 3: cross-over mating (control X control; control X high dose (each opposite sex)
Task 4: second generation evaluation
administration route: specified as % in feed or drinking water
See chapter 5.8
Result: Task 2:
reduced mean number of pups born alive at all dose levels, reduced proportion of pups born alive at 0.15 and 0.3% and decreased mean life pup weight per litter (both sexes) at 0.3%.
Task 3:
at the tested dose of 0.3% (510 mg/kg) reduced proportion of female pups born alive, reduced mean and adjusted mean live weight per litter (females)
Test substance: theophylline; according to the authors, purity was >99% (analyzed)
Reliability: (2) valid with restrictions
10-MAR-2003 (107)

Species: mouse **Sex:** female
Strain: ICR
Route of administration: i.p.
Exposure period: one of gestation days 10 - 13
Frequency of treatment: single injection
Doses: 100, 150, 200 mg/kg be/d
Control Group: yes, concurrent no treatment

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

Method: i.p. application to the animals on day 10, 11, 12, 13.

Result: A dose-related increase of resorptions and malformations occurred with a peak embryotoxic response in fetuses treated on day 11. Malformations that occurred were mainly cleft palate but also polydactyly, ectrodactyly, syndactyly and micromelia. According to the authors, the test substance was slightly embryotoxic and strongly teratogen.
Test substance: theophylline
Reliability: (3) invalid
No results of the control group reported; study does not meet current standards (i.e. ip. application)
10-MAR-2003 (108)

Species: mouse **Sex:** female
Strain: ICL-ICR
Route of administration: i.p.
Exposure period: day 12 of gestation
Frequency of treatment: single injection
Doses: 175, 200, 225 mg/kg
Control Group: yes, concurrent vehicle

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

Remark: NOEL for maternal toxicity cannot be given since data were insufficiently reported; study does not meet current standards
Result: About 40% of the high-dose females died. Dyspnea and convulsions were observed at 175 and 200 mg/kg. Fetal body weight was decreased at 200 and 225 mg/kg. Malformations occurred dose-dependently in all fetuses, and included cleft palate, digital defects and macrognathia. Subcutaneous hematomas were also observed.
Test substance: theophylline
Reliability: (3) invalid
20-NOV-2001 (109)

Species: rabbit **Sex:** female
Strain: other: Kbl::JW
Route of administration: i.v.
Exposure period: day 6-18 of gestation
Frequency of treatment: continously with infusion pump
Duration of test: up to day 29 of gestation
Doses: 15, 30, 60 mg/kg bw/day
Control Group: yes
NOAEL Maternal Toxity: 30 mg/kg bw
NOAEL Teratogenicity: 30 mg/kg bw

Method: other: japanese guideline
Year: 2000
GLP: no data
Test substance: other TS

Result: In the highest dose group a significant decrease in body weight was observed from gestation day 11 onwards, and a decrease in food intake was noted during days 7-23.

Theophylline showed reversible toxicity: accelerated respiration, sluggish startle reactions, dilatation of the auricular vessels and polyuria in dams treated with 60 mg/kg/day, but not in dams given 15 and 30 mg/kg/day. Fetuses from the dam group treated with 60 mg/kg/day exhibited teratogenic toxicity such as cleft palate and, also, skeletal variation of the 13th rib. Fetal toxicity was also observed including abortion, increased number of late deaths and decreased body weight appearing on day 29 of gestation. No toxicity was observed in fetuses from the 15 and 30 mg/kg/day group. In the 15, 30 and 60 mg/kg/day groups, maternal plasma concentrations (Cmax) during the treatment period were approximately 30, 56 and 106 µg/ml, respectively. These concentrations clearly exceed the effective therapeutic range of theophylline in clinical use. NOAEL fetotoxicity 30 mg/kg/day.

Test condition: Theophylline was injected into the auricular vein of 20 animals/group at a volume of 20 ml/kg using an automatic infusion pump at a rate of 0.5 ml/kg/min once daily from day 6-18 of gestation. Body weight was recorded on days 2,5-19,21 23, 25, 27, 29 of gestation.
The numbers of implantations and live fetuses were counted on day 29.
Toxicokinetic determination of theophylline was determined on 3 animals/dose and the plasma concentrations were analyzed using HPLC method.

Test substance: theophylline

Reliability: (2) valid with restrictions
sufficient details were not given

Flag: Critical study for SIDS endpoint

10-MAR-2003 (110)

Species: mouse **Sex:** female
Strain: no data
Route of administration: oral unspecified
Exposure period: days 4 to 16 of gestation
Frequency of treatment: daily
Duration of test: until day 19 of gestation
Doses: 5.25, 100 mg/kg bw/d
Control Group: no data specified

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

Result: The teratogenic activity of the test substance was evaluated. Mice were administered the test substance on days 4 to 16 of gestation. Fetuses were investigated on day 19 of gestation. Reproductive health of the dams, as well as external and skeletal malformations of the fetuses were determined. According to the authors, no teratogenic effect was seen after oral administration of the test substance at a dose levels corresponding with the therapeutic dose.

Test substance: theophylline

Reliability: (4) not assignable
only short abstract available

10-MAR-2003 (111)

Species: mouse **Sex:** female
Strain: ICL-ICR
Route of administration: s.c.
Exposure period: day 11 of gestation
Frequency of treatment: single dose
Duration of test: until day 18 of gestation
Doses: 46.4 mg/kg
Control Group: yes, concurrent vehicle

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

Result: The aim of the study was to investigate the synergism in the teratogenicity of the test substance and mitomycin C when administered simultaneously. The test substance was administered subcutaneously, mitomycine was administered intraperitoneally; both compounds were dissolved in saline. On day 11 of gestation, 11 mice received saline (s.c. and i.p.; vehicle controls); 15 mice received theophylline and saline (i.p.); 33 mice received saline (s.c.) and mitomycin C; and 20 mice received theophylline and mitomycin C. On day 18 of gestation, the mice were sacrificed. The number of implantations and resorptions, fetal weights and the incidence of malformation were determined.
Significant changes were seen only in the group administered both componds: fetal weight was decreased; the incidence of malformed surviving fetuses was 80% compared with 0.8%, 2.7% and 3.8% in the group administered saline, theophylline alone, and mitomycin C alone, respectively. The most frequent malformations were cleft palate, micrognathy and digital defects.
According to the authors, these results suggested that neither theophylline nor mitomycin C was teratogenic when administered alone and that combined administration of the two compounds resulted in a marked teratogenic effect.
Test substance: theophylline
Reliability: (3) invalid
combination with mitomycin C, not anough animals with theophylline alone
06-FEB-2003 (112)

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 theophylline comprises thousands of published studies and reviews due to 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, Stavric, 1988, and Ogilvie, 1978 and studies cited in these reviews were

selected for the data set of theophylline. Relevant recent publications have also been taken into account.

23-JUL-2001

Remark: kinetics (absorption, distribution, metabolism and excretion)

Theohylline is rapidly absorbed after an oral dose. Absorption can be delayed by food while aging has no effect on the rate or extent of absorption.
Peak serum levels are generally achieved after 1.5-2 hours. At 17 ug/ml, 56% has been bound reversibly to adults' plasma protein compared to 36% in cord plasma from infants. Reduction in protein binding is observed during the last two trimesters of pregnancy. Theophylline does not accumulate in any specific target organs. It is distributed in erythrocytes and breast milk, but not extensively in adipose tissue. It passes the amniotic fluid. The presence of a blood-brain barrier reduces theophylline concentrations in the brain. A cerospinal fluid : plasma ratio of 0.68 has been reported. Elimination half-life is 15-60 h in premature infants (2-4 weeks post partum) and 3.4 h in children aged 1-4 years; the values for adults exhibit large variations and range from 3-11 h. Clearance increases by 10% over the age range 1-15 years. In persons aged 60 years and above, half-lives of 5.4-9.0 h are recorded. Smokers have decreased elimination half-lives compared to non-smokers (4 vs 7 h). The use of contraceptives lowers plasma clearance and increases the elimination half-life while plasma binding and volume of distribution is unaffected. The volume of distribution ranges from 0.44-0.51 in both adults and children.
Volume of distribution and elimination half-life is increased during the third trimester of pregnancy. Elimination is dose-dependent; however, linear pharmacokinetics is a valid model within the therapeutic range. Nonlinearity may be due to metabolic saturation or to the diuretic effect.
Seven to 12% is excreted unchanged in the urine. Several parallel pathways produce 3-methylxanthine (9-18%), 1-methylxanthine (0.4.4%), 3-methyluric acid (traces), 1-methyluric acid (13-16%), and 1,3-dimethyluric acid (35-55%; main metabolite). Methylation to caffeine occurs to some extent in adults, and is the predominant pathway in neonates. Dietary factor modify the elimination in children and adults. Serum protein levels follow a circadian rhythm, but these effects are less pronounced than interindividual variations that are predominantly under genetic control.

23-JUL-2001 (113) (114) (115)

Remark: kinetics (absorption, distribution, metabolism and excretion)

Twenty asthmatic adults received appr. 7.5 mg/kg bw theophylline i.v. over 30 min.; 10 of these patients tablets and the remainder solution in a similar dose. The fraction

of the dose absorbed averaged 0.96 +- 0.03 for the tablet while the value for the solution was 0.99 +- 0.02. The time of peak absorption av. 2 +- 0.3 hours for the tablets and 1.4 +- 0.3 hours for the solution. The maximun serum concentration attained was 15.3 +- 0.7 µg/ml after a dose of
7.6 +- 0.4 mg/kg of the tablet, and 14.6 +- 0.6 µg/ml after a dose of 7.3 +- 0.2 mg/kg of the solution. Absorption of the tested theophylline tablets and solution approached 100 % of the available drug.

23-JUL-2001 (116)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The influence of various test meals, and of fluid volumes, on the bioavailability of theophylline from a solid dosage form has been studied in six healthy subjects. Absorption of
drug was faster after dosing immediately following a high protein meal than after a high fat or a high carbohydrate meal. Absorption from a solution was faster than from a solid dosage form in all treatments; areas under serum level
time curves after dosing were also significantly higher up to 12 hr. Areas up to 12 hr after dosing also tended to be higher after the high protein meal and after dosing with 500 ml water on an empty stomach than after other solid dose treatments.

17-MAY-2001 (117)

Remark: 16 premature infants suffering from neonatal apnoea received
orally an aqueous solution of theophylline 5 mg/kg bw under fasting conditions and immediately before a milk feed. The rate of absorption was significantly decreased if the drug was given with food; mean maximum serum concentrations were reached after 4.7 h instead of 1.6 h under fasting conditions. The area under the curve did not differ between the two patient groups which indicates that only the rate but not the amount of absorption was affected by food intake.
kinetics (absorption, distribution, metabolism and excretion)

20-FEB-2001 (118)

Remark: An av. 96% of an uncoated theophylline tablet is absorbed, with peak conc. occurring from 0.5 to 2.0 h. In plasma, some
53 to 65% of theophylline is reversibly bound to protein. Theophylline is distributed to erythrocytes, saliva, breast milk and can cross the maternal placenta. The appr. volume of distribution in the steady state av. 0.5 l/kg bw. Theophylline is eliminated by biotransformation in the liver
and urinary excretion of its metabolites. Appr. 7 to 13% is excreted unchanged in the urine by a first order process. The plasma theophylline conc. time curve after i.v. administration fits a 2 compartment open kinetic model with

a rapid distribution phase completed within 30 to 45 minutes
after an i.v. dose. The ß-elimination phase is quite variable and in healthy adults ranges from 3 to 13 h. The elimination of theophylline is markedly decreased in premature infants and increased in childhood. The volume of distribution is ranged from about 0.45 to 0.52 l/kg. Plasma theophylline conc. of 5 to 20 mg/l can produce concentration related increases in forearm blood flow and reductions in cerebral blood flow.
Serious adverse effects are rare at plasma theophylline concentrations below 20 mg/l. The most frequent effects involve the gastrointestinal system (anorexia, nausea, vomiting, abdominal discomfort) and the nervous system (headache, nervousness, anxiety), which usually occur with concentrations over 15 mg/l. Between 20 and 40 mg/l, sinus tachycardia and atrial or ventricular arrhythmias occur with
increasing frequency. Above 40 mg/l, focal or generalised seizures, or cardiorespiratory arrest can occur.
kinetics (absorption, distribution, metabolism and excretion, review)

23-JUL-2001 (119)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Theophylline concentrations were measured in six apneic premature infants after i.v. infusion. Theophylline´s apparent volume of distribution was 0.60 l/kg, and half-life was 30.2 h. Blood clearance rate (17.6 ml/kg/h) was lower than plasma clearance rate of young children. At a total plasma concentration of 17 mg/l, 56 and 36% of the theophylline was bound to adult or full-term cord plasma proteins, respectively.

16-MAR-2001 (120)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Theophylline half-life after single oral dose was investigated using saliva drug measurements. 19 healthy subjects received theophylline doses of 3-5 mg/kg bw per oral. The mean saliva/serum theophylline ratio was 0.46. The correlation coefficient was 0.33-0.81.

23-JUL-2001 (121)

Remark: Distribution of theophylline into breast milk was investigated in five women. The average milk to serum concentration ratio of the drug was about 0.7 and milk concentrations parallel the time-course of serum and saliva concentrations. On a relative body weight basis, a nursing infant would usually receive less than 10% of the mother´s dose of theophylline.
kinetics (absorption, distribution, metabolism and excretion)

23-JUL-2001 (122)

Remark: An acute theophylline intoxication in a 17-month-old female child was reported. Peak serum theophylline level was 102.4

µg/ml. Some spinal fluid (CSF) was retained and the concentration was 32.5 µg/ml and the CSF/plasma ratio was 0.68.
kinetics (absorption, distribution, metabolism and excretion)

23-JUL-2001 (123)

Remark: kinetics (absorption, distribution, metabolism and excretion)
On a multiple-dose schedule of oral theophylline (200 to 300 mg every 6 hours) serum theophylline in 83 patients ranged from 2.9 to 32.6 µg/ml. Elimination half-life ranged from 181 to 571 minutes.

23-JUL-2001 (124)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The kinetics of theophylline (3-5 mg/kg bw) was examined in a group of nonsmokers and in heavy smokers. The elimination half-life in smokers averaged 4.3 hr., significantly shorter than the mean value for nonsmokers (7.0 hr.). The apparent volume of distribution was somewhat larger in smokers (0.50 l/kg) than in nonsmokers (0.38 l/kg). The body clearance was appreciably larger and relatively more variable in smokers (100 ml/min/1.73 m2) than in nonsmokers (45 ml/min/1.73 m2).

23-JUL-2001 (125)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The kinetics of theophylline was studied in 6 normal, nonsmoking male subjects. A constant-rate i.v. infusion of 3.84 to 4.98 mg/kg bw of theophylline was administered over 40 min. Within 30 min. The serum levels reached 10 µg/ml. The highest serum level at the end of the infusion was 17 µg/ml. Ther serum concentration-time data were fitted to a two-compartment open model and yielded a mean serum elimination half-life of 11.02 hr.

23-JUL-2001 (126)

Remark: In a group of 19 hospitalized patients, most of whom smoked, the elimination half-life of theophylline following an i.v. bolus (5 mg/kg bw) was 3.6 hours. A control group of 10 smokers had a elimination half-life of 4.1 and 14 nonsmokers a elimination half-life of 7.2 hours.
kinetics (absorption, distribution, metabolism and excretion)

22-FEB-2001 (127)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The effect of chronic oral contraceptive (OC) usage on the disposition of theophylline was examined. 4 mg/kg was given to 8 healthy female OC-users and 8 nonusers. The OC users

had a significantly lower total plasma clearance of theophylline than women not using OC (35.1 vs. 53.1 ml/h/kg). The half-life time was also significantly prolonged in the OC group (9.79 vs. 7.34 h) while the volume of distribution was similar between the two groups.

23-JUL-2001 (128)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The influence of oral contraceptives (OCS) and sex differences on the disposition of theophylline has been studied in 12 helathy young men, 13 healthy young women, and 10 healthy young women receiving OCS. The elimination half-life was longer in women taking OCS (523 min.) than in women not on OCS (386 min.) Weight normalized plasma clearance of theophylline was less in women taking OCS steroids (0.70 ml/min/kg) than in women not on OCS (0.98 ml/min/kg). Weight normalized clearance, volume of distribution, plasma elimination half-life and plasma binding were not different between men and women not taking OCS.

23-JUL-2001 (129)

Remark: Dose-dependent kinetics was studied in 20 children with chronic asthma receiving iv. infusion of theophylline. The initial infusions resulted in steady-state serum concentrations ranging from 6.2 to 18 µg/ml and later to 15.7 to 30.8 µg/ml. Clearances at the lower infusion rates ranged from 0.71 to 2.13 ml/kg/min. At the higher dose clearance av. only 1.21 ml/kg/min.
kinetics (absorption, distribution, metabolism and excretion)

22-FEB-2001 (130)

Remark: After a single dose the major sources of nonlinearity are saturable hepatic metabolism and time-dependent changes in renal clearance of theophylline. At steady state, renal clearance is constant and nonlinearity is apparently related only to saturable metabolism.
kinetics (absorption, distribution, metabolism and excretion, review)

17-MAY-2001 (131)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The total plasma and partial metabolic and renal clearance of theobromine and theophylline were determined in 13 healthy subjects. Clearance by N-demethylation at the 3-position was 3.7-fold higher (unbound clearance 2.5-fold higher) for theobromine than for theophylline, showing that the position of the other methyl substitutent (position 1 or 7) is a major determinant of metabolic rate. Major metabolites are 1,3-dimethyluric acid (49.1%), 1-methyluric acid (24.5%), and 3-methylxanthine (17.5%).

23-JUL-2001 (132)

Remark: kinetics (absorption, distribution, metabolism and excretion)

Plasma concentration of theophylline and caffeine in seven premature neonates receiving theophylline for treatment of apnea were measured. Plasma concentration of caffeine increased from 1.8 mg/l at day one to 3.7 mg/l seven days after initiation of theophylline therapy. Plasma concentration of theophylline were 4.6 mg/l and 11.0 mg/l on day one and day 7 of theophylline therapy. In contrast, in four normal adult subjects receiving theophylline no measurable caffeine concentrations were found. The metabolic pathway followed by theophylline in premature infants includes a methylation reaction producing caffeine, whereas adults, the major metabolic pathway involves oxidative reactions (demethylation and oxidation).

22-FEB-2001 (133)

Remark: Caffeine and its major metabolites, paraxanthine, were observed in plasma following oral administration of theophylline in a multiple dose study. At steady state, plasma caffeine concentration varied from 0.21 to 0.75 mg/l at plasma theophylline concentrations of 8.1 to 21.5 mg/l in four healthy subjects. About 6 % of the theophylline dose was converted to caffeine.
kinetics (absorption, distribution, metabolism and excretion)

23-JUL-2001 (134)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The effect of diet on theophylline metabolism was examined in 14 children receiving long-term theophylline administration for asthma. Compared to the normal diet, high protein diet markedly decreased the elimination half-life, and high carbohydrate diet greatly prolonged it.

16-MAR-2001 (135)

Remark: Effect of an increase in dietary lipids on metabolism of theophylline was examined 9 subjects. Isocaloric substitution of fat for carbohydrate produced little or no significant change in the mean plasma elimination half-life (7.9 h on both diets).
kinetics (absorption, distribution, metabolism and excretion)

22-FEB-2001 (136)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Polymorphism of theophylline metabolism was examined in 79 unrelated adults, six sets of monozygotic twins, six sets of dizygotic twins and six two-generation families. The twin study revealed predominantly genetic control. Values for this genetic component of interindividual variation in rate constants of metabolite formation were 0.61, 0.84, and 0.95 for 3-methylxanthine, 1-methyluric acid, and 1,3-dimethyluric acid. In the 79 unrelated adults, each distribution curve for rate constants of formation of each theophylline metabolite appeared to be trimodal. By contrast, the distribution curve for the overall theophylline elimination rate constant appeared to be

either unimodal or bimodal. The extent of interindividual variation was fourfold for theophylline elimination constant and 6-8-fold for three principal metabolites. In each of the six families the rate constants were consistent with their control by two alleles at a single genetic locus and with autosomal codominat transmission. Frequencies of the two alleles at each genetic locus controlling rate constants of formation of theophylline metabolites were similar.

23-JUL-2001 (137)

Remark: kinetics (absorption, distribution, metabolism and excretion)
Theophylline kinetics were studied serially in five women during and after pregnancy. Theophylline protein binding was reduced to 11.1% and 13.0% during the second and third trimesters of pregnancy, repectively, compared with 28.1 when the patients were more than 6 months postpartum.

Similar comparisons indicate that theophylline distribution volume and elimination half-life were increased from 30.7 and 262 minutes to 36.8 and 389 minutes in the third trimester of pregnancy. In the second and third trimesters, intrinsic nonrenal clearance was reduced to 0.82 ml/min/kg and 0.67 ml/min/kg compared with a remote postpartum value of 1.25 ml/min/kg.

27-FEB-2001 (138)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The influence of age, sex, and smoking on theophylline disposition was studied in 38 healthy subjects ranging in age from 26 to 81 yr. There were 8 young and 30 geriatric subjects, including 28 men and 10 women. A single dose of theophylline elixir (5 mg/kg bw) was given as a reference to all subjects and two sustained-release (SR) tablets (8 and 6 mg/kg bw). Theophylline elimination half-life is shorter in the geriatric group (6.93 and 8.14 h); total body theophylline clearance is greater in the geriatric group (44.39 and 32.97 ml/kg/hr), and the apparent volume of distribution is also greater in the geriatric group (26.29 and 22.97 l). In 93% of the geriatric subjects, serum theophylline levels of 8 to 20 µg/ml were reached at steady state with the SR tablet.

23-JUL-2001 (139)

Remark: kinetics (absorption, distribution, metabolism and excretion)
The two-compartment kinetics of theophylline in ten hospitalized elderly patients with apparently normal renal, hepatic and cardiopulmonary functions was investigated after intravenous administration of the drug. Biological theophylline elimination half-lives of 5.4-9.0 hours and plasma clearance values of 28-42 ml/kg/hr. were found. The apparent volumes of distribution during the ß-phase, were 0.33-0.43 l/kg.

23-JUL-2001 (140)

Remark: general toxicity (review)
Toxicity can be produced easily owing the narrow therapeutic index. A small percentage of patients taking theophylline therapeutically to control asthma may develop toxicity at serum levels of 20-30 ug/ml, while no effcts were seen at levels <15 ug/ml. Administration to premature babies in the preterm period caused sleep disturbances that persisted after the substance had been cleared.
No differences were found at one or two years of age as a function of treatment in the preterm period, while the question whether theophylline affects learning ability in children remains open. Mild toxicity may include headache, gastrointestinal disturbances, hypotension, irritability, and insomnia.
Severe symptoms include tachycardia, arrhythmia, cardiac arrest, and serious neurological symptoms and seizures. Deaths have also been reported.

26-FEB-2001 (114) (115)

Remark: general toxicity (review)
Toxic effects include tachycardia, dysrhythmia, emesis, death, osmotic diuresis, failure to gain weight, necrotizing enterocolitis, hyperglycemia, tremor, diuresis/dehydration, jitteriness, cardiac arrhythmias, seizures, nausea/vomitting, mood disturbances, and hypotension. Peak serum theophylline concentrations correlate with the severity of toxicity.
Oral administration of multiple doses of activated charcoal is recommended for nearly all patients with theophylline intoxicaation since charcoal increases theophylline clearance. Hemoperfusion is recommended in severely intoxicated patients.

23-JUL-2001 (141)

Remark: Despite the use of theophylline for over 50 years, the actual mechanism of action is unkown. Currently adenosine antagonism is discussed. Theophylline stimulates the central nervous system; has positive inotropic and chronotropic effects on the heart; causes diuresis; relaxes smooth muscle; increases serum catecholamine levels; increases striated muscle contractility; causes peripheral vasodilation (but cerebral vasoconstriction); increases gastric secretions; and increases lipolysis, glycogenolysis and glucogenesis. The most common clinical manifestations of theophylline toxicity are gastrointestinal (i.e., nausea, vomiting, diarrhea, abdominal pain, and bleeding), cardiovascular (i.e., various tachydysrhythmias, hypotension, and cardiac arrest), and neurologic (i.e., irritability, tremor, lethargy, seizures, and coma). Toxic symptoms usually appear at theophylline levels of 20-25 mg/l and usually increase in both frequency and severity with increasing levels. Major toxicity (seizures, hypotension, serious dysrhythmias, and cardiac arrest) generally does not occur until serum levels are extremely elevated (i.e., >60 mg/l). toxic effects (review)

23-JUL-2001 (142)

Remark: Hospital laboratory records of 163 cases study toxicity in children with theophylline serum concentrations of >133 µmol/l. Symptoms were absent in 44 patients with theophylline concentrations of 139 to 278 µmol/l; concentrations of >278 µmol/l were always associated with symptoms. The most common clinical symptoms were tachycardia (47%) and vomiting (52%). Nine patients had seizures, including five who were previously neurologically normal.
toxic effects

23-JUL-2001 (143)

Remark: Sixty-four cases of theophylline poisoning after ingestion of sustained release preparations prescribed for asthma were reviewed. Serum theophylline levels were 365 µmol/l (mean).
Electrolyte and metabolic abnormalities (hypokalaemia, hypomagnesaemia, hypophosphataemia, hyperglycaemia, acid-base disturbances and leucocytosis) were common. Serum potassium, serum glucose, leucocyte count and length of stay in the intensive care unit all correlated strongly with maximum serum theophylline level. The low incidence of life-threatening manifestations of severe toxicity (hypotension, serious arrhythmias or seizures) and excellent outcome, contrasts with many previous reports.
toxic effects

23-JUL-2001 (144)

Remark: A case of attempted suicide with theophylline in a 50-year-old depressive woman was reported. Theophylline levels peaked at 148 mg/l. On admission at the hospital the patient was comatose and she developed several generalized convulsive episodes. The physical examination revealed tachypnea, dyspnea, and peripheral cyanosis. There were three episodes of ventricular tachycardia and fibrillation. The patient was awake 12 h after admission, and recovered uneventfully during the next few days.
toxic effects

23-JUL-2001 (145)

Remark: A comprehensive summary of reports of theophylline-induced toxicities between 1980 and 1990 is provided. The major of the adverse effects occur in two categories: neurologic and cardiovascular symptoms and side effects. Although the majority of the neurologic side effects were symptoms, 198 patients had seizures as a result of theophylline. Arrhythmias were the most frequent cardiovascular complication, with 525 patients having some abnormal conduction, ranging from sinus tachycardia to ventricular tachycardia or fibrillation. There were 63 deaths reported. Among the toxicities for which an etiology was noted, 184 were therapeutic misadventures, 125 were accidental ingestions, and 114 were suicidal overdosage. Of cases where serum theophylline concentrations were reported, 109 toxicities were in the range of 20 to 40 µg/ml and 168 toxicities were associated with serum concentrations greater than 40 µg/ml. Thirty-three cases had concentrations greater than 100 µg/ml. Adverse effects associated with

concentrations less than 20 µg/ml were reported in 69 patients.
toxic effects
26-FEB-2001 (146)

Remark: Theophylline is widely prescribed in the treatment of airways obstruction, usually in the form of sustained release preparations. Its therapeutic use may be associated with significant morbidity. This is largely a result of the drug´s narrow therapeutic index and variable interindividual pharmacokinetics and pharmacodynamics, together with the influence of concurrent medication and disease.
Adverse effects in therapeutic usage, acute and chronic overdosage of theophylline were reviewed. Theophylline toxicity principally affects the gastrointestinal, cardiovascular and central nervous systems. There may also be characteristic metabolic disturbances.
In addition, deliberate or accidental overdosage may result in serious toxicity after a latent period of hours, and the outcome may be fatal.
The accepted therapeutic serum concentration of theophylline ranges from 10-20 µg/ml, although improvement in forced respiratory volume in 1 s (FEV1), vital capacity and airways resistence have been demonstrated at plasma concentrations as low as 4-5 µg/ml.
toxic effects (review)
31-AUG-2001 (147)

Remark: The newborn´s potential for xanthine toxic reactions from placental transfer of theophylline or caffeine conversation from theophylline was studied in 12 newborns of asthmatic mothers. Newborn theophylline levels ranged from 2.3 to 19.6 µg/ml. Side effects in three babies with levels of theophylline greater than 10 µg/ml were tachycardia and transient jitteriness.
toxic effects
16-MAR-2001 (148)

Remark: Nine cases of theophylline poisoning in adults were reported. There was a fivefold variation in plasma theophylline concentrations, which in general correlated poorly with the stated ingested dose. Signs of severe toxicity, such as hypotension and cardiac arrhythmias, were common in patients aged over 50, whereas three of the younger patients with high plasma theophylline concentrations (69 mg/l, 50.2 mg/l, and 64.2 mg/l) had only minimal symptoms. Convulsions occurred in three patients. Tachycardia was noted in all cases, and hypotension occurred in four. All three deaths were associated with plasma theophylline concentrations exceeding 65 mg/l, convulsions, hypotension, and finally cardiorespiratory arrest. toxic effects
23-JUL-2001 (149)

Remark: Case report of two fatal cases after acute ingestion of theophylline (100 Aminophylline tablets and appr. 10 g oxtriphylline). Blood theophylline concentrations were 260 and 290 mg/l.

toxic effects
26-FEB-2001 (150)

Remark: Theophylline intoxication was reported in four asthmatic patients. Three arrived in status asthmaticus; their admission blood levels were 33, 48, and 68 µg/ml. The other had persistent vomiting; blood level was 46 µg/ml.
toxic effects
26-FEB-2001 (151)

Remark: Symptoms, course, and treatment of 10 patients with severe theophylline toxicity (heart rate above 120, multifocal atrial tachycardia or premature ventricular contractions, hypotension, seizures) were described. Theophylline levels at presentation averaged 66 µg/ml.
toxic effects
16-MAR-2001 (152)

Remark: toxic effects
Two cases of seizure activity due to theophylline overdose with serum levels of 26 and 26.3 µg/dl were reported. Both patients had evidence of prior neurologic damage.

23-JUL-2001 (153)

Remark: A follow-up study of 35,909 outpatients who filed more than 220,000 prescriptions for theophylline over 9 years
revealed
30 hospitalizations for xanthine toxicity. The overall estimated incidence rate of 7.8/10,000 person-years at risk indicates that in this population hospitalization for xanthine toxicity is a relatively rare event.
toxic effects
28-FEB-2001 (154) (155)

Remark: A retrospective chart audit was done in 40 consecutive
adult
inpatients to identify preventable factors contributing to theophylline toxicity. Toxicity was produced in 27 of 40 patients by inpatient or emergency department theophylline administration. Management errors found included delay (>10 hours) in taking action from time toxic blood levels were drawn (20 patients), inappropriately high dosing of patients with congestive heart failure (17 patients), failure to recognize obvious symptoms (16 patients), recurrent toxicity (11 patients), additional emergency department treatment of already toxic patients (7 patients), overlap of intravenous and oral therapy (6 patients), patient discharged with no physician awareness of toxicity or dosage change (5 patients).
toxic effects
23-JUL-2001 (156)

Remark: The objective of a 67-month prospective study conducted on 249 consecutive patients in Massachussetts, USA, was to identify patients at high risk for major toxicity after theophylline intoxication who might benefit from early charcoal hemoperfusion.
One hundred and nineteen patients (48%) not receiving theophylline therapy had acute intoxications; among those receiving such therapy, 92 (37%) had theophylline intoxication because of chronic overmedication, and 38 (15%) had acute intoxication. Major toxicity developed in 65 patients (25%), 13 patients (5%) died. Major toxicity was more common in patients with intoxication due to chronic overmedication than in those with acute intoxication who were not receiving therapy (49% vs. 10%, risk ratio = 4.85 (95% CI 2.96-7.94)), even though the former group had lower serum theophylline levels (283 umol/l vs. 777 umol/l). Logistic regression analysis identified two major factors associated with the development of major toxicity: 1) peak serum theophylline concentrations in cases of acute intoxication and 2) patient age in cases of chronic overmedication. Receiver-operating characteristic curve analysis indicated that major toxicity occurred in patients with a peak serum concentration of >555 umol/l (ca. 100 mg/l) after acute intoxication and in patients older than 60 years (regardless of peak serum theophylline concentration) after chronic overmedication.
According to the author, these results suggested that predictors for major toxicity after theophylline intoxication differ by the type of overdose.
toxic effects

26-FEB-2001 (157)

Remark: Recommended therapeutic per oral dose is 11-13 mg/kg BW in adults and 18-24 mg/kg BW in children.
toxic effects (review)

06-SEP-2001 (158)

Remark: A dietary case-control study of 854 histologically diagnosed cases of benign breast disease (BBD), 755 matched surgical controls, and 723 matched neighborhood controls was conducted. The estimated mean intake of methylxanthines was similar for cases and controls (302, 312, and 313 mg for cases, surgical controls, and neighborhood controls). No association between methyxanthine intake and BBD was observed.
toxic effect (benign breast disease)

23-JUL-2001 (159)

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 effect (benign breast disease)

23-JUL-2001 (160)

Remark: Complete triploidy was found in lymphocyte cultures from a stillborn full-term female infant with a birth weight of 1,000 g. The child had a ventricular septal defect of the heart but no other macroscopic internal or external malformations. The mother, who had a history of prolonged anti-asthmatic medication (ephedrine, phenobarbitone, diphenylhydramine and theophylline), displayed a high incidence of satelite associations and chromatid breakages in her cultured lymphocytes.
mutagenicity

23-JUL-2001 (161)

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 was evaluated 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)

23-JUL-2001 (162)

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.

16-MAR-2001 (163)

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.

16-MAR-2001 (164)

Remark: Data collected in the Collaborative Perinatal Project were assessed for association of theophylline intake and risk of stillbirth in a total sample of 51,830 singleton pregnancies. Theophylline ingested by pregnant women does not appear to increase their risk of delivering a stillbirth. reproductive/developmental toxicity

(stillbirth)
17-MAY-2001 (165)

Remark: In a retrospective study drug consumption during pregnancy of mothers of infants with congenital abnormalities were compared with those without. Over 97% of 1,369 mothers took prescribed drugs and 65% self-administered drugs. No differences were evident between the two groups concerning intake of theophylline.
reproductive/developmental toxicity (anomalies)
17-MAY-2001 (166)

Remark: reproductive/developmental toxicity (fetal effects)
The relation between maternal administration of theophylline and fetal breathing movements during late gestation was investigated. Seventeen women with normally grown fetuses at 33-38 weeks' gestation were given 400 mg of sustained-release theophylline orally after a 1-hour control period. Maternal plasma theophylline and glucose concentrations were measured every hour; the incidence of fetal breathing movements and breathing rates were measured continuously during the following 8 hours. Results were compared with those of a similar control group (untreated). Maternal plasma concentrations were significantly increased; mean glucose levels were unchanged during the first 6 hours and then slightly decreased. The incidence of fetal breathing significantly increased while the mean hourly breathing rate was not significantly altered. According to the authors, these results suggested that ingestion of theophylline by pregnant women in the late gestation is associated with an increase in fetal breathing movements.
23-JUL-2001 (167)

Remark: developmental toxicity (fetal effects)
The toxic fetal effects of theophylline are described in two case-reports. Fetal effects included transient tachycardia, irritability, and vomiting. Maternal serum concentrations were in the high therapeutic range.
23-JUL-2001 (168)

Remark: developmental toxicity (neonate)
The development of premature infants treated with theophylline in the neonatal period of apnea was examined. The theophylline-treated infants had lower Apgar scores and gestational ages when compared to those who did not receive theophylline. There were no significant differences in the developmental indices, and both groups had similar incidences of severe neurologic sequelae and retrolental fibroplasia. Similarly, there were no differences in the somatic growth. Theophyline does not adversely affect development of premature infants when examined at 9-27 months if age.
23-JUL-2001 (169)

Remark: developmental toxicity (neonate)
No harmful effects of neonatal methylxanthine therapy on cognitive function was seen when neurodevelopmental outcome of 73 very-low-birthweight neonates at 18 months with

respect to the presence of germinal matrix and/or intraventricular hemorrhage and neonatal methylxanthine therapy was analyzed.

23-JUL-2001 (170)

Remark: reproductive/developmental toxicity (infant)
The relationship between theophylline therapy and outcome at 14 years of age in surviving preterm children of birthweight <1501 g was determined in 154 consecutive survivors from 1980-1982. Outcomes included motor function, psychological test scores, and growth. The rate of cerebral palsy was significantly higher in children exposed to theophylline compared to children not exposed. In contrast children who had received theophylline achieved higher psychological test scores. There was no association between theophylline therapy and growth.

17-MAY-2001 (171)

5.11 Additional Remarks

Type: adsorption

Result: In humans, the test substance was readily absorbed after ingestion (ca. 96%) with maximum plasma concentrations being reached within 30-120 minutes. In contrast, the test substance was absorbed slowly after intramuscular injection.

Test substance: theophylline

05-SEP-2000 (172) (173)

Type: Biochemical or cellular interactions

Result: The competitive inhibition of cyclic nucleotide phosphodiesterase activity by the test substance was studied. The test substance inhibited the enzyme that catalyses the breakdown of the intracellular messenger cyclic 3',5'-adenylic acid (cAMP) to 5'-adenylic acid (AMP). The accumulation of cAMP increased the action of neurotransmitters and hormones that were mediated by intracellular cAMP (for instance of catecholamine). The test substance also inhibited certain purine nucleoside phosphorylases.
In vitro, the test substance inhibited beef heart cGMP phosphordiesterase activity in a dose-dependent manner. The IC50 (e.g. the concentration giving a 50% inhibition) was 2.91 mM (ca. ca. 524 mg/l) at 50 uM cGMP.

Test substance: theophylline

05-SEP-2000 (174)

Type: Biochemical or cellular interactions

Result: The electrophysiological effect of the test substance was studied.
High levels of the test substance triggered the release of norepinephrine, causing an increase in the number of slow Ca2+-channels available for voltage activation through which Ca2+ could pass during the action potential. This mobilization of Ca2+ affected the sleketal muscle and neuromuscular synaptic transmission and stimulated the release of catecholamine from the adrenal medulla. Increased

Ca2+ resulted in electrolyte changes, cardiac arrhythmia, hypotension and gastrointestinal disturbances. Combination of elevated cAMP and potentiation of catecholamine and other hormones caused relaxation of smooth muscle (mainly of the bronchi and blood vessels). According to the authors, these interactions as well as direct effects of Ca2+ on the contractile apparatus of the heart were considered to be responsible for the cardiac effects of the test substance.

Test substance: theophylline

05-SEP-2000 (175)

Type: Biochemical or cellular interactions

Result: Genotoxic effects of the test substance were summarized. The test substance was incorporated into DNA and interferred with normal DNA synthesis, mitosis, and postreplication DNA repair.
The effects of the test substance were presumed to be exerted by inhibiting DNA synthesis, mitosis and DNA repair.

Test substance: theophylline

23-JAN-2001 (176) (177) (178)

Type: Biochemical or cellular interactions

Result: Male Wistar rats and female Sprague-Dawley rats were fed a diet containing 1.39 g/kg (1390 ppm) of the test substance (ca. 65 mg/kg). Increased calcium excretion by greater than 300% of control was observed.

Test substance: theophylline

05-SEP-2000 (179)

Type: Chemobiokinetics general studies

Remark: Mean half life (T1/2) after single i.v. application of 9.4 mg/kg to dogs was 5.7 h and the specific volume of distribution was 0.82 l/kg. After oral application of 9.4 mg/kg, the bioavailability was about 91% and the absorption half life (T1/2 abs.) was 0.4 h with a peak plasma concentration of 8.4 ug/ml at 1.5 h.

Test substance: theophylline, tested as aminophylline

05-SEP-2000 (180)

Type: Chemobiokinetics general studies

Remark: Single i.v. injection of 13.8 and 52 mg/kg to male guinea pigs resulted in mean plasma concentrations between 1.5 - 33 ug/ml (low dose) and 9.1 - 77 ug/ml (high dose). The clearence was 2.02 and 1.50 ml/min/kg (low and high dose). Single i.v. injection of 52 mg/kg in pretreated animals (44.3 mg/kg, i.p. twice daily for 12 days) resulted in an increased elimination.

Test substance: theophylline, tested as aminophylline (pure)

16-AUG-2000 (181) (182)

Type: Chemobiokinetics general studies

Remark: The effect of intra-arterially doses of 1.3, 2.6, 5.0, 10.0 and 20.0 mg/kg was investigated in male Wistar rats. The elimination half lifes (t1/2 el.) were 71, 58, 75, 68 and 67 min, the AUC were 10, 17, 46, 129 and 410 min/mg/l x 100 and the clearences were 5.9, 6.8, 4.8, 3.7 and 2.6 ml/min/kg. No differences were observed in the capacity limited elimination of the two major metabolites 1,3-dimethyluric acid and 1-methyluric acid. The initial apperent first order decay after higher doses resulted from a combination of capacity limited metabolism and compensatory increased diuresis of unchanged theophylline. Linear pharmacokinetics in rats apply only to doses not exceeding 10 mg/kg.

Test substance: theophylline

05-SEP-2000 (183)

Type: Chemobiokinetics general studies

Remark: I.p. injection of 10 mg/kg to virgin, pregnant (day 19-20 of gestation) and lactating (nursing for 7 days prior to treatment) female Charles River rats resulted in an elimination half life (t1/2 el.) of 3.2, 4.9 and 3.2 h, the clearence was 139, 103 and 165 ml/h/kg, respectively.

Test substance: theophylline

05-SEP-2000 (184)

Type: Chemobiokinetics general studies

Remark: Absorption, distribution, metabolism and excretion in animals:
Theophylline is rapidly and completely absorbed from the digestive tract of dogs. Large variations in its bioavailability were found in pigs, while complete bioavailability is reported in cats and rats. After i.v. administration it is distributed to all organs of rats except adipose tissue. After oral administration radio-labelled theophylline showed no accumulation in any specific tissue after 24 h. By 1 h after oral application itcrossed the placenta and is distributed among the fetal and pregnant rat organs except for the brain of the adults and low concentrations were found in fetal brain indicating thatno blood-brain barrier exists. Similar results found after i.v. injection to rats and in rabbits. Serum binding was lower in dogs (10%) than in man (60%) and rabbits (74%) and less in pregnant rats (6%) than in non-pregnant rats (20%). A significant increase in the half-life was found in pregnant as compared to non-pregnant rabbits, while the half-life in newborn rabbits was about 15 times longer than in adult animals. It is rapidly distributed within the body and plasma half-lifes ranged between 1.2 - 11.5 h (min. for rats and max. for dogs) for several species. At higher doses(52-115 mg/kg) rats had longer half-lifes due to increased diuresis and saturation of the metabolism. Theophylline is metabolized in the liver, mainly by the microsomal system and oral doses of 40 mg/kg/day for three

days did not induceliver microsomal enzyme activity. The pathway of metabolism in rats is that unchanged theophylline and 1,3-dimethluric acid are the main compounds excreted in urine, followed by 1-methyluric acid, 3-methylxanthine and unidentified polar metabolites. Impairment in metabolism was recorded for pregnant rats and baboons. Each species is characterized by differences in the profile of urinic metabolites and differences in metabolism were seen in different strains of mice (IARC, 1991). For further reviews or detailed studies see McManus et al., 1988; McKiernan et al., 1983; Ingvast-Larsson et al., 1992; Sanvordeker et al., 1977; Gabrielsson et al., 1984; Arnaud et al., 1982; Brashear et al., 1982; El-Yazigi and Sawchuk, 1981.

Test substance: theophylline

05-SEP-2000 (185) (186) (187) (188) (3) (189) (190) (191) (192)

Type: Chemobiokinetics general studies

Remark: The effect of aging on the pharmacokinetics and biotransformation was examined in Mongolian gerbils aged 30-39 (old), 12-18 (middle-aged) and 3 (young) months following a 20 mg/kg i.p. injection. Plasma kinetics showed decreased clearence, increased half-life and increased volume of distribution in old vs. young animals; clearence to 1,3-methyluric acid was similar, while that to 1-methyluric acid was lower in the middle-aged group. Urinary recovery of 1-methylurate was increased in old vs. young and middle-aged, while recovery of theophylline was decreased. Decreased microsomal protein content was observedin old vs. young and middle-aged animals and an age-related decrease in cytochrome P-450 content was also observed.

Test substance: theophylline, tested as aminophylline (highest grade commercially available)

16-AUG-2000 (193)

Type: Chemobiokinetics general studies

Result: In rats, the test substance was metabolized to 1,3-dimethyluric acid and 1-methyluric acid. 3-Methylxanthine was not detected. The biological half-life was 6 +/- 1.5 hours (determined from urinary excretion). The half-life in the blood was 3.5 hours. The metabolic rate of the test substance was increased by induction of hepatic drug-metabolizing actitivy.

Metabolism of the test substance was considered to occur solely by liver microsomal P-450 enzymes. There was no evidence in the heart, lung, intestine, brain, adrenal glands, kidneys, or spleen. Pretreatment with the test substance, 3-methylcholanthrene increased the metabolic rate, indicating induction of metabolic enzymes. Plasma half-lives of the test substnce were lowered by inducers, such as 3-methylcholanthrene or phenobarbital.

Test substance: theophylline

05-SEP-2000 (194) (195) (196)

Type: Chemobiokinetics general studies

Result: Several studies on chemobiokinetic data of the test substance in humans were summarized.

Maximum plasma concentration was found at 56 minutes after oral administration of 300 mg or 20 minutes after intravenous injection of 240 mg.

The test substance was reversibly bound to plasma proteins and distributed in erythrocytes, saliva, breast milk and amniotic fluid. The test substance was able to cross the placenta, accumulated in the fetus and was eliminated slowly.

The clearance of the test substance was reduced by antidepressants (viloxazine, fluvoxamine), calcium antagonists (nifedipine, verapamil, diltiazem), H2-receptor antagonists (cimetidine, famotidine), oral contraceptives and antibiotics (erythromycin, ciprofoxacinm allopurinol). The clearance was increased by phenytoin, phenobarbitone, mexiletine, tobacco smoking and marihuana smoking.

Test substance: theophylline

24-JAN-2001 (53)

Type: Chemobiokinetics general studies

Remark: The effect of age was determined after i.v. (ca. 4 mg/kg) injection to dogs at 1, 2, 3, 4, 8, 12, 16, 24, 52 and 104 weeks of age. Younger dogs had a slower elimination half life (1 week t1/2: 987 min) than 8 weeks old dogs (t1/2: 138 min). The values plateaued until 16 weeks of age and then increased slightly of up to t1/2: 219 min in 104 weeks old dogs. A similar pattern was obtained for the clearance (1 week old: 1.17 ml/min/kg; 16 weeks old: 7.09 ml/min/kg; 104 weks old: 3.5 ml/min/kg). Volume of distribution was not significant different and ranged between 1.2 to 1.6 l/kg.

Test substance: theophylline, tested as aminophylline

05-SEP-2000 (197) (198)

Type: Cytotoxicity

Remark: The cytotoxicity was determined in rat hepatocytes, McCoy and MDBK cells; the respective CT50 values were 2.175; 14.56; 5.549 mM. 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.

Test substance: theophylline

05-SEP-2000 (199)

Type: Cytotoxicity

Remark: The acute in vitro cytotoxicity was assayed biochemically inhuman lymphocytes and resulted in LC50 values of 2900 µg/ml (LDH assay), 3350 mg/ml (DNA assay) and 3150 µg/ml (MTT assay). The IC50 value for HeLa cells was 440 µg/ml.

Test substance: theophylline

05-SEP-2000 (200)

Type: Cytotoxicity

Remark: Cytotoxicity was determined in human foreskin fibroblast cell line (HEF), human hepatoma cell line (HepG2), human melanoma cell line (Mel/27), human epidermal keratinocyzes (NHEK) and in human endothelial cells (ENDO) using the neutral red assay. The following midpoint cytotoxicity values (NR50%) were determined:
ENDO: 9 mM
NHEK: 18 mM
HEF: 20 mM
Mel/27: 18 mM
HepTG2: 19 mM

Test substance: theophylline

05-SEP-2000 (201)

Type: Immunotoxicity

Remark: Concentrations in the range of 0.1 - 1 uM decreased the Con A blastogenic response of spleenic C57Bl mouse cells and the NK activity of spleenic CBA mice in vitro. After i.p. injection of 75 and 100 mg/kg for 5 days to male mice the NK activity was also slightly reduced.

Test substance: theophylline

05-SEP-2000 (202)

Type: Metabolism

Remark: Percutaneous absorption and metabolism was examined in vitrousing human skin. Diffusion ranged between about 2.2 - 7.7%,but absorption varied to a large extent between the different skin samples (3.6 - 33.4 %). Between 0.2 - 4.6% were metabolized and over 60% of the metabolites diffused through the skin. Biotransformation by microsomes to 1,3,7-trimethyluric acid, 1,3-dimethyluric acid and 3-methylxanthine occurred in a varying extent.

Test substance: theophylline (radiolabelled); according to the authors, purity was >98%

14-AUG-2000 (203)

Type: Metabolism

Result: The metabolism of the test substance in humans was summarized.
Within the therapeutic range, the test ubstance was

metabolized first-order kinetics. At high concentrations, metabolic enzymes became saturated and zero-order became evident. The test substance was converted to 1,3-dimethyluric acid, 3-methylxanthine, and 1-methylxanthine which was further metabolized to 1-methyluric acid. The test substance was metabolized by the liver mixed-function oxidase system using more than one cytochrome P-450 isoform. The metabolites were excreted unchanged in the urine. The test substance was also detected in human urine.
Conversion of the test substance to caffeine did not occur; however, conversion of caffeine to theophylline had been reported.

Test substance: theophylline

05-SEP-2000 (204) (205) (206) (207)

Type: Metabolism

Remark: Kinetics and metabolism of theophylline in animals have been reviewed by IARC, (1991). It is rapidly and completely absorbed from the digestive tract and distributed to all organs of rats except adipose tissue. It readily crosses the placenta and no blood-brain barrier was observed. Plasma half-life is between 1.2-4 hours in rats and 6-11.5 hours in dogs and strongly dependent on protein binding and dose. Theophylline is metabolized in the liver, mainly by the microsomal system. The metabolites are excreted into the bile and eliminated with the urine.

Flag: Critical study for SIDS endpoint

11-SEP-2001 (208)

Type: other

Remark: Pharmacokinetic studies in rats revealed a mean plasma half-life of 5 h which was unaffected by repeated exposure. A dose of 25 mg/kg resulted in plasma levels similar to those observed in humans receiving a therapeutic dose.

Test substance: theophylline

05-SEP-2000 (209) (210)

Type: other

Remark: The test substance induced reverse transformation in Chinese hamster ovary R1 cells.

Test substance: theophylline

05-SEP-2000

Type: other

Remark: The test substance delayed the onset and reduced the rate of DNA replication in synchronized HeLa S-3 cells but not as a direct result of inhibition of DNA synthesis.

Test substance: theophylline

05-SEP-2000 (211)

Type: other

Remark: Doses of greater than 0.3 mg/ml inhibited DNA synthesis in mouse L5178Y cells, LS929 mouse fibroblasts and V79 Chinese hamster cells. Reduction of newly synthesized DNA was inhibited in both unradiated and ultraviolet radiated cells.

Test substance: theophylline

05-SEP-2000 (212)

Type: other: carcinogenicity screening

Remark: In a screening assay for liver carcinogens male F 344 rats received initially a single i.p. injection of diethylnitrosamnie and two weeks later the compound at 8000 ppm applied via the drinking water; theophylline was proved to be negative since no induction of GST-P positive foci occurred.

Test substance: theophylline

05-SEP-2000 (213)

Type: other: cell transformation

Result: The test substance interferred with the transformation of epithelial cells in culture by dimethylbenz(a)anthracene to cellular DNA.

Test substance: theophylline

05-SEP-2000 (214)

Type: other: inhibition of neoplasia

Result: The test substance inhibited the development of skin neoplasms induced by ultraviolet light. According to the authors, this possibly reflected an ability of the test substance to inhibit error-prone post-replication DNA repair (Zajdela and Latarjet, 1978).
Partial supression of neoplasm production had also been reported by Reddi and Constantinides (1978).

Test substance: theophylline

05-SEP-2000 (215) (178)

Type: other: periarteritis in rats

20-NOV-2001

Type: other: review (mutagenicity)

Remark: Literature reviews of papers on general or selective mutagenicity tests

23-JAN-2001 (216) (217) (73) (218) (66) (219)

Type: other: teratogencity (chick embryo)

Remark: In the in vitro teratogenicity screening assay using the whole chick embryo culture the IC50 was around 0.4 mmol/l (concentration that induced malformations in 50% of the embryos).

Test substance: theophylline

23-JAN-2001 (220)

Type: other: teratogenicity (chick embryo)

Result: The teratogenic activity of the test substance was evaluated in vitro. Chick embryos were exposed to the test substance (0.001-1 mmol/l; ca. 0.1-180 mg/l) for 2 days during the early stages of organogenesis (gastrula and neurula). Fifteen embryos were used per dose level. Survival and morphogenesis of the nervous, cardiovascular and skeletomotor system and of the extraembryonic membranes were recorded. According to the authors, the test substance was of a low embryotoxicity; malformations were observed at concentrations of 0.1, 0.5. and 1 mmol/l (ca. 18, 90, and 180 mg/l, respectively). Mainly cerebral vesicles, heart, rotation, and cervical flexure were affected.

Test substance: theophylline

24-JAN-2001 (111)

Type: other: teratogenicity (chick embryo)

Result: The teratogenicity of the test substance was studied in chick embryos. Leghorn eggs were incubated at 37 degree Cand windowed on day 3 of incubation. When the embryos had developed to stage 26, they were treated with the test substance. The test substance was dissolved in saline; 2.5, 3.8, and 5.0 mg was applied topically to the extraembryonic membranes of 53, 50, and 25 eggs, respectively. Two hundred and forty-one untreated and 164 saline-treated eggs were used as normal and vehicle controls, respectively. The embryos were subsequently reincubated, harvested after 14 days of incubation and examined for external anomalies. Mortality rate was 4.6%, 9.8%, 9.4%, 40.0%, and 72.0% in the untreated control, vehicle control, low dose, mid dose, and high dose group, respectively. The test substance retarded growth in a dose-dependent manner (8.3%, 36.7%, and 42.9% at the low, mid and high dose level, respectively vs. 0.4% and 0.7% in untreated and vehicle controls, respectively). Beak malformations were seen in 57,1% of the surviving high dose group embryos; no malformations of the beak were seen in the other four groups. Generalized edema was noted in 10% and 100% of the surviving mid and high dose embryos, respectively. No malformations of the limbs were observed in any group.
According to the authors, these results demonstrated that the test substance retarded embryonic growth and produced generalized edemas and beak malformations.

Test substance: theophylline

24-JAN-2001 (221)

Type: other: teratogenicity (chick embryo)

Result: The teratogenicity of the test substance was studied in chick embryos. Leghorn eggs were incubated at 37-38 degree Centigrade. When the embryos had developed to stage 26, they were treated with the test substance. The test substance was dissolved in saline; 14, 21, and 28 umoles (ca. 2.5, 3.8, and 5.0 mg, respectively) to 48, 29, and 27 eggs, respectively; saline was applied to 176 control eggs. All embryos were examined for cardiovascular malformations (aortic arch anomalies).
The test substance did not significantly alter the incidence of aortic arch anomalies; malformation rate was 0/27 at the low and mid dose level, 1/48 (2%) at the high dose level, and 2/176 (1%) in controls.
However, the test substance significantly enhanced anomalies of the aortic arch induced by catecholamines (norepinephrine or epinephrine). Following coadministration of the test substance (14 and 21 umol; ca. 2.5 and 3.8 mg, respectively) and 4 nmol of either norepinephrine or epinephrine, the incidence of aneurysm in the ascending aorta of the embryos was significantly increased when compared with the incidence of malformations induced by the catecholamine alone; this enhancement was dose-dependent. The effective dose of norepinephrine was potentiated more than 100 times; the effective dose was potentiated more than 2 times.
According to the authors, these results suggested that the test substance, at doses which were not teratogenic, enhanced the teratogenicity of catecholamines.

Test substance: theophylline

24-JAN-2001 (222)

Type: other: teratogenicity (frog larvae)

Result: The teratogenic activity of the test substance was studied in frog (Xenopus laevis) larvae according to the protocol of the frog embryo teratogenesis assay - Xenopus (FETAX). In addition, the synergism of the teratogenic activity of the test substance and inhibitors of DNA synthesis (hydroxyurea and cytosin-arabinoside), protein synthesis (5-fluoruracil and cycloheximid) and nucleic acid synthesis (emetin) was evaluated. Treatment with the test substance alone (160 larvae, tretment period: 96 hours; only one dose level tested) produced growth retardation, increased mortality and increased incidence of malformations in surviving larvae when compared with untreated controls. Coadministration of the test substance with each inhibitor greatly enhanced the incidence of malformed embryos.

Test substance: theophylline

23-JAN-2001 (223)

Type: other: toxic effects

Result: Myocardial lesions were observed in male and female

Sprague-Dawley rats after i.p. injection of 150 mg/kg of the test substance. Ninety per cent of the rats died within 20 to 25 minutes after injection.

Test substance: theophylline

05-SEP-2000 (224)

Type: other: toxic effects (human)

Result: A strong correlation between toxic effects and blood concentration was found in a study of 47 hospitalized individuals. Toxic symptoms were common at serum concentrations over 25 ug/ml; no symptoms were observed at concentrations lower than 15 ug/ml. The most common symptons were gastrointestinal (nausea, vomitting, diarhhea). In individual patients, agitation (1 person), tremors (1 person), seizure (1 person), and tachycardia (2 persons) were observed.

Test substance: theophylline

05-SEP-2000 (225)

Type: other: toxic effects (human)

Result: The test substance increased the urinary output of magnesium, calcium and sodium and decreased serum levels of phosphate.

Test substance: theophylline

05-SEP-2000 (226)

Type: other: toxic effects (human)

Result: Clinical features of the test substance included metabolic disturbances, and effects on the gastrointestinal, cardiovascular, and central nervous system.

Test substance: theophylline

05-SEP-2000 (206) (227)

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 the handling of chemicals must be observed.
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (2)

8.2 Fire Guidance

Ext. Medium: Suitable extinguishing media: water, dry extinguishing media, carbon dioxide (CO2), foam
Add. Information: Further information: Dispose of fire debris and contaminated extinguishing water in accordance with local regulations.

Remark: Thermal decomposition: 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