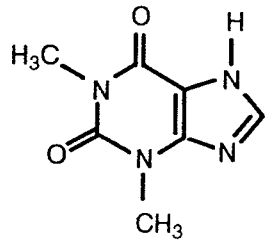
THEOPHYLLINE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 58-55-9
Chem. Abstr. Name: 3,7-Dihydro-1,3-dimethyl-1*H*-purine-2,6-dione
Synonym: 1,3-Dimethylxanthine

1.2 Structural and molecular formulae and molecular weight



$C_7H_8N_4O_2$ Mol. wt: 180.17

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: White crystalline powder (Moffat, 1986)
(*b*) *Melting-point*: 270-274°C (Windholz, 1983)
(*c*) *Spectroscopy data*: Ultraviolet spectra: aqueous acid-270 nm (A_1^1 = 536a), aqueous alkali-275 nm (A_1^1 = 650a); infrared spectra: principal peaks at wave numbers 1670, 1717, 1567, 745, 980 and 1190 (potassium bromide disc); mass spectra: principal peaks at *m/z* 180, 95, 68, 41, 53, 181, 96, 40; 3-methylxanthine, 166, 68, 95, 41, 53, 123 (Moffat, 1986)
(*d*) *Solubility*: Soluble in water (1.0 g/120 ml), ethanol (1.0 g/80 ml), chloroform (1.0 g/110 ml), hot water, alkali hydroxides, ammonia and dilute hydrochloric and nitric acids; sparingly soluble in diethyl ether (Windholz, 1983)

(*e*) *Equilibrium constants*: acidic (Ka), 1.69×10^{-9}; basic (Kb), 1.9×10^{-14} at 25°C (Windholz, 1983)
(*f*) *Octanol/water partition coefficient (P)*: log P, 0.0 (Moffat, 1986)
(*g*) *Reactivity*: Solutions generally quite stable over the entire pH range; strongly alkaline solutions (pH > 12) show decomposition and apparent ring opening after several weeks (Cohen, 1975)

1.4 Technical products and impurities

Theophylline is available in a USP grade with the following specifications: 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; 0.15% max residue on ignition; and melting-point, 270-274°C (US Pharmacopeial Convention, 1990). Theophylline should contain not less than 99.0% and not more than 101.0% active ingredient on a dried basis (Anon., 1988).

Trade names: Accurbron; Aerolate; Afonilum; Aquaphyllin; Armophylline; Asthmophylline; Bronchoretard; Bronkodyl; Duraphyl; Elixicon; LaBid; Lasma; Nuelin; Optiphyllin; Oralphyllin; Physpan; Primatene; Pro-vent; Quibron-T; Rona-Phyllin; Slixophyllin; Slo-Bid; Slo-Phyllin; Somophyllin-T; Sustaire; Teofilina; Thealtabl; Theobid; Theocap; Theocin; Theoclear; Theocontin; Theocord; Theodel; Theodrine; Theo-Dur; Theofed; Theofedral; Theograd; Theolair; Theolate; Theolixir; Theoliz; Theon-300; Theophenyllin; Theophyl; Theophyl-SR; Theoral; Theosol; Theospan; Theostat; Theovent; Unicontin; Uniphyllin. It is also an ingredient of Franol; Franyl; Labophylline; Phyldrox; Quibron; Tancolin; Taumasthman; Tedral (Moffat, 1986)

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Theophylline has been prepared from dimethylurea and ethyl cyanoacetate (Windholz, 1983).

The production of theophylline derivatives in the USA in 1977 amounted to 51 000 kg and total US imports of theophylline and its derivatives in 1978 were 590 000 kg (Haley, 1983a). Domestic production data were not reported for 1981-86; however, on the basis of the total imports of food and beverages containing methylxanthines into the USA in 1980, 185 million pounds (84 million kg) of tea

containing 0.03% theophylline were imported, resulting in approximately 60 000 pounds (27 000 kg) of theophylline (Hirsh, 1984). Five companies in the USA were reported to produce theophylline or theophylline derivatives in 1986 (SRI, 1986). US imports of theophylline, theophylline ethylenediamine and their derivatives in January to June 1989 amounted to approximately 825 000 kg (US Bureau of the Census, 1989).

Data were not available from other parts of the world.

(*b*) *Use*

Theophylline and its monohydrate, aluminium hydroxide, choline (oxtriphylline), calcium salicylate, ethylenediamine (aminophylline), dihydroxypropyl (dyphylline), monoethanolamine and sodium glycinate derivatives (Weinberger, 1978) are used to control asthmatic symptoms, to relieve bronchial spasms, to alleviate neonatal apnoea (Stavric, 1988), in the treatment of respiratory diseases, such as bronchitis, obstructive pulmonary disease and emphysema, as a myocardial stimulant, to relieve biliary colic and in diuretics (Ritchie, 1975; Stavric, 1988; Barnhart, 1989). The doses used are 180-1000 mg per day (Moffat, 1986), which result in 10-20 μg/ml plasma.

Theophylline is also administered in combination with ephedrine, guaifenesin, butabarbital and phenobarbital (Gennaro, 1985; Moffat, 1986; Consumers Union, 1990). Sodium and potassium salts and a large number of less basic salts and/or complexes have been prepared in order to increase the water solubility of theophylline for parenteral administration (Cohen, 1975). More than 200 different theophylline preparations exist in the USA as prescription or over-the-counter drugs and fewer than 100 in Canada (Weinberger, 1978; Stavric, 1988). In the USA in 1986, over 11 million prescriptions were written for the theophylline drug, Theo-Dur (Anon., 1986). In 1985, over 25 million prescriptions were written for theophylline-containing medications in the USA (Collins, 1987). In the USA in 1980, theophylline was ranked twentieth among the 100 most prescribed drugs.

2.2 Occurrence

(*a*) *Natural occurrence*

Theophylline occurs in black tea (*Camellia sinensis*) at very low levels; values cited in the literature vary greatly, but the most reliable range is 0.02-0.04% dry weight (Jalal & Collin, 1976; Graham, 1984a). Theophylline has been found in green coffee beans at approximately 5 mg/kg (Spiller, 1984), and trace amounts were detected in cacao cotyledon (Shively & Tarka, 1984). Theophylline was detected at 0.004% in dried mate (Graham, 1984b).

(*b*) *Occupational exposure*

A national occupational hazard survey conducted in the USA in 1972-74 estimated that approximately 7500 people were exposed occupationally to theophylline (National Institute for Occupational Safety and Health, 1974). No occupational standard has been established for theophylline.

(*c*) *Water and sediments*

Theophylline was not found in US industrial effluents (Perry *et al.*, 1979) or drinking-water (National Research Council, 1977) or in European water supplies (Commission of the European Communities, 1976).

(*d*) *Foods and beverages* (see also the monograph on caffeine, pp. 296 *et seq.*)

Theophylline was detected in blended black tea beverages at a level of 0.25% of the extractable solids present (Graham, 1984a). In the USA in 1980, 26 000 pounds (11 800 kg) of theophylline were consumed, as estimated from an importation of 185 million pounds of tea containing an average of 0.03% theophylline, equal to 60 000 pounds and a preparation and extraction loss of 50%. The total daily per-caput intake of theophylline in the USA was estimated to be 0.14 mg (Hirsh, 1984).

2.3 Analysis

The techniques and analytical procedures for theophylline and other methylxanthines have been reviewed (Cohen, 1975; Christensen & Neims, 1984; Hurst *et al.*, 1984; Christensen & Neims, 1985; Stavric, 1988).

A large variety of analytical procedures, including spectrophotometry, fluorimetry, thin-layer chromatography, gas chromatography, high-performance liquid chromatography, radioimmunoassay, enzyme immunoassay and isotachophoresis have been employed for the determination of theophylline (and concomitant separation from other methylxanthines and metabolites) in biological fluids and dosage formulations. Earlier procedures primarily involved ultraviolet spectrophotometry with a sensitivity ranging from 1-10 μg/ml in plasma (Schack & Waxler, 1949; Gupta & Lundberg, 1973) and 2-15 μg/ml in dosage formulations (Kirichenko & Kagan, 1970); but these methods lacked specificity. Gas chromatographic procedures for the analysis of theophylline are more sensitive and more selective, in that interfering xanthines are separated from theophylline; in general, however, these methods require more sample preparation and derivatization. The sensitivity of detection is 1 μg/ml theophylline in plasma, serum or saliva (Chrzanowski *et al.*, 1974; Shah & Riegelman, 1974; Johnson *et al.*, 1975). High-performance liquid chromatography procedures are sensitive and specific

and generally require smaller amounts of biological fluids; they are used extensively for monitoring theophylline levels (Hurst *et al.*, 1984; Christensen & Neims, 1985; Stavric, 1988) in serum or plasma (Adams *et al.*, 1976; Orcutt *et al.*, 1977; Soldin & Hill, 1977; Broussard *et al.*, 1981; Muir *et al.*, 1982; Matsumoto *et al.*, 1988; Meatherall & Ford, 1988) and urine (Muir *et al.*, 1980; Kester *et al.*, 1987) of treated patients. Sensitivities of 1 μg/ml (Adams *et al.*, 1976), 5 μg/ml (Broussard *et al.*, 1981), 8 μg/ml (Soldin & Hill, 1977), 20 μg/ml (Orcutt *et al.*, 1977) and 0.5 μg/ml plasma or saliva (Muir *et al.*, 1982) and 0.15 μg/ml urine (Kester *et al.*, 1987) have been obtained using high-performance liquid chromatography. In all of the commonly used clinical procedures, detection was accomplished by ultraviolet spectrophotometry at wavelengths of 254, 270-277 or 280 nm (Christensen & Neims, 1985).

Additional procedures for the determination of theophylline in biological fluids include fluorimetry (Meola *et al.*, 1979), substrate-labelled fluorescent immunoassay (Messenger *et al.*, 1980; Li *et al.*, 1981a,b; Lee & Liberti, 1987), enzyme multiplied immunoassay (Gushaw *et al.*, 1977; Eppel *et al.*, 1978; Chang *et al.*, 1982), automated fluoroimmunoassay (Allain *et al.*, 1989), homogeneous enzyme-inhibitor immunoassay (Chan *et al.*, 1987), radioimmunoassay (Neese & Soyka, 1977), nephelometric inhibition immunoassay (Nishikawa *et al.*, 1979), isotachophoresis (Moberg *et al.*, 1980) and ion-exchange chromatography (Walton *et al.*, 1979). Sensitivities ranged from 10 μg/ml by fluorimetry (Meola *et al.*, 1979) to 0.7 μg/ml by substrate-labelled fluorescent immunoassay (Li *et al.*, 1981a), 1 μg/ml by automated fluoroimmunoassay (Allain *et al.*, 1989) and 10 ng or less by ion-exchange chromatography (Walton *et al.*, 1979).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

No data were available from studies on the carcinogenicity of theophylline.

Modifying effects on the activity of known carcinogens

(i) *Urethane*

Groups of female ICR/Jcl *mice* [initial numbers unspecified], 25 days of age, received a single subcutaneous injection of 0.1 mg/g bw urethane followed immediately by seven intraperitoneal injections (0.05 μmol/g bw) of theophylline

[purity unspecified] at 6-h intervals up to 36 h after urethane treatment, to give a total dose of 63 μg/g bw theophylline. Mice were killed five months after urethane treatment. No significant difference was noted in the numbers of mice with lung tumours (31/59 controls compared to 25/43 mice that received theophylline) or in the numbers of tumours/lung (1.07 compared to 1.36) (Nomura, 1983). [The Working Group noted that the effective numbers of mice varied considerably among the different groups.]

(ii) *Ultraviolet light*

Groups of 54-56 female nonhomozygous Swiss *mice*, 10-12 weeks old, were exposed to the light from an Ellipiol mercury vapour lamp (irradiation time, 90 min) five times a week for a total of 133 exposures over 27 weeks (total dose, 1×10^7 ergs/mm2). Before each irradiation, 40 μl of a 0.2% solution of theophylline [purity unspecified] in acetone/chloroform were applied to the right ear; the same amount of solvent was applied to the left ear as a control. The first tumours of the ears appeared five months after and the last 11 months after the onset of irradiation. The incidence of tumours on the ears treated with theophylline (48%) was significantly ($p < 0.0001$) lower than that of the control ears (85%) (Zajdela & Latarjet, 1973, 1974, 1978a,b).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, metabolism and excretion*

The metabolism and pharmacokinetics of theophylline have been reviewed (Arnaud, 1984).

Theophylline was rapidly and completely absorbed from the digestive tract of dogs (McKiernan *et al.*, 1981; Tse & Szeto, 1982). Large variations in its bioavailability were reported in pigs (Koritz *et al.*, 1981) while complete bioavailability was found in cats and rats (Arnaud *et al.*, 1982; McKiernan *et al.*, 1983).

Transport of theophylline from blood to the intestinal lumen was demonstrated in rats (Arimori & Nakano, 1985). After intravenous administration, theophylline was distributed to all organs of rats except adipose tissue (Shum & Jusko, 1984). Whole-body autoradiographs showed no accumulation of radioactivity in any specific tissue 24 h after oral administration of [8-^{14}C]theophylline to rats. By 1 h after oral administration, theophylline had crossed the placenta and was distributed among the organs of fetuses and of pregnant rats, except for the brain of adults. Low theophylline concentrations were found in fetal brain; no blood-brain barrier was observed (Arnaud *et al.*, 1982).

Similar results were found after intravenous administration to rats (Gabrielsson *et al.*, 1984). In rabbits, transplacental transfer of theophylline from maternal to fetal circulation occurred within less than 1 h (Brashear *et al.*, 1982).

Mean serum protein binding of theophylline was lower in dogs (10%) than in man (60%) and rabbits (74%) (Brashear *et al.*, 1980; May & Jarboe, 1981; Munsiff *et al.*, 1988a), and less was bound in pregnant rats [6%] than in non-pregnant rats [20%] (Ramzan & DeDonato, 1988). Similarly, a significant increase in the half-time of theophylline was found in pregnant as compared to non-pregnant rabbits (Brashear *et al.*, 1982) and rats (Brandstetter *et al.*, 1986). The half-time in newborn rabbits was approximately 15 times longer than that in adult animals (Brashear *et al.*, 1982).

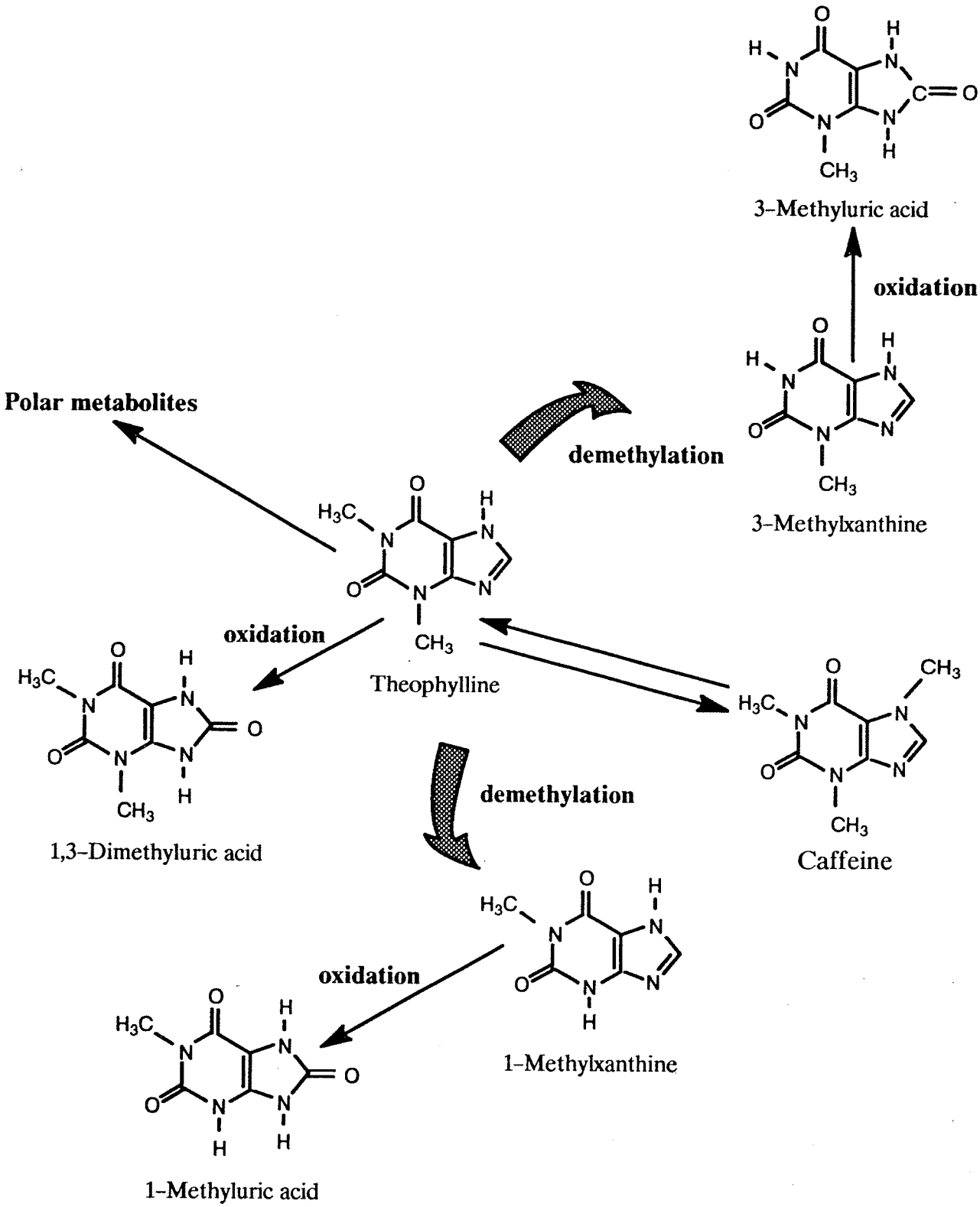
Theophylline is distributed rapidly within the body, and plasma half-times were 5.7-11.5 h in dogs (Barnhart & Combes, 1974; McKiernan *et al.*, 1981), 11 h in pigs (Koritz *et al.*, 1981), 7.8 h in cats (McKiernan *et al.*, 1983), 3.8-5.5 h in rabbits (Ng & Locock, 1979; May & Jarboe, 1981) and 1.2-4 h in rats. At higher doses (52-115 mg/kg bw), rats had longer half-times probably because of a combination of increased diuresis and saturation of the metabolism (Teunissen *et al.*, 1985).

Linear pharmacokinetics apply in rats only with intra-arterial doses not exceeding 10 mg/kg bw (Teunissen *et al.*, 1985); similar results were obtained in guinea-pigs (Madsen & Ribel, 1981a,b). In rabbits, there was no evidence of concentration-dependent clearance of theophylline at 15, 22.5 and 30 mg/kg bw (El-Yazigi & Sawchuk, 1981). The clearance and disposition were unchanged in rats with dietary induced obesity (Shum & Jusko 1984).

Theophylline is metabolized only in the liver, mainly by the microsomal system (Lohmann & Miech, 1976; McManus *et al.*, 1988). In rats, oral doses of 40 mg/kg bw per day for three days did not induce liver microsomal enzyme activity, as measured by aromatic ring hydroxylation of acetanilide (Mitoma *et al.*, 1968), while doses of 75-150 mg did.

The pathways of theophylline metabolism reported in rats are presented in Figure 1. Unchanged theophylline (35% of urinary radioactivity) and 1,3-dimethyluric acid (34%) are the main compounds excreted in urine, followed by 1-methyluric acid (18%), 3-methylxanthine (3%) and unidentified polar metabolites (4.8%). Theophylline metabolism was impaired in rats at day 18 of gestation, as shown by increased excretion of theophylline (73%); this was explained by a decreased formation of 1,3-dimethyluric acid (-68%) and 1-methyluric acid (-30%) (Arnaud *et al.*, 1982). Essentially similar results were obtained with pregnant baboons (Logan *et al.*, 1983). Each animal species is characterized by differences in

Fig. 1. Metabolism of theophylline



[a]From Arnaud (1984)

the profile of the metabolites recovered in urine; in addition, quantitative differences in theophylline metabolic pathways were seen even in different strains of mice (Betlach & Tozer, 1980).

Experiments in hepatectomized dogs have shown that the liver plays a central role in theophylline elimination (Brashear *et al.*, 1980). Theophylline and its metabolites are excreted into the bile; in rats, 0.2% (Arimori & Nakano, 1985) and in dogs, 2-4% (Barnhart & Combes, 1974) of the dose was recovered.

(ii) *Toxic effects*

The acute intraperitoneal LD_{50} of theophylline in rats was reported to be 206 mg/kg bw, and accompanying clinical signs were delayed convulsions and tetanic spasm. Acute studies in mice showed an oral LD_{50} of 332 mg/kg bw and an intraperitoneal LD_{50} of 217 mg/kg bw; clinical signs included convulsions, profuse salivation and emesis (Tarka, 1982).

A single oral dose of 400 mg/kg bw theophylline was acutely toxic to rats and mice. Administration of the same daily dose as two separate doses of 200 mg/kg bw was acutely toxic to rats but not to mice (Lindamood *et al.*, 1988). In dogs, the minimal oral toxic concentration of theophylline appears to be higher (37-60 μg/ml plasma) than in man (> 20 μg/ml) (Munsiff *et al.*, 1988b). Theophylline has been reported to be more toxic than caffeine or theobromine to the heart, bronchi and kidneys (Tarka, 1982).

Two weeks' feeding 800 ppm (mg/kg) theophylline in the diet to rats induced no significant toxicity except for dose-related uterus hypoplasia (Lindamood *et al.*, 1988).

(iii) *Effects on reproduction and prenatal toxicity*

Reproductive toxicity: Feeding theophylline to immature (five to six weeks old) Osborne-Mendel rats at 0.5% in the diet [approximately 300 mg/kg bw per day] for 75 weeks produced severe testicular atrophy in 50% of animals, oligospermatogenesis and aspermatogenesis. These results were confirmed in Holtzman rats fed 0.5% theophylline for 19 weeks: 86% showed testicular atrophy (Friedman *et al.*, 1979).

In 13-week toxicity studies, weanling $B6C3F_1$ mice and Fischer 344 rats were administered theophylline by gavage or in the diet. Gavage with 300 mg/kg bw per day led to a slight but significant decrease in testicular weight in mice, but 150 mg/kg bw or less had no effect. In rats, a significant decrease in testicular weight was observed after gavage with 150 mg/kg bw per day but not with 75 mg/kg bw or less. No effect on sperm motility, sperm density or the number of abnormal sperm was observed in male rats or mice, and no effect was seen on the mean length of the oestrous cycle in females. Daily administration of 184-793 mg/kg bw theophylline in

the diet to mice had no effect on sperm, whereas abnormal sperm were seen in rats given 258 mg/kg in the diet but not at lower doses (Morrissey *et al.*, 1988).

In a reproductive study, Swiss CD-1 mice were administered 0.075, 0.15 or 0.30% theophylline in the diet (average daily doses, 125, 265 or 530 mg/kg bw) for one week before mating and during 13 weeks of cohabitation. Litters were removed one day after birth, except for the last litter which was raised to 21 days of age. Among all treated groups, there was a dose-related decrease in the number of live pups per litter; in the high-dose groups, there was a significant decrease in the number of litters per breeding pair and a significant decrease in live pup weight. In the high- and mid-dose groups, a significant decrease in the percentage of pups born alive was observed. Only mild toxicity was observed in adults at these doses. In a cross-over mating trial at the end of a 19-week exposure to 0.3% theophylline, animals of each sex were found to be affected, although females were more severely affected than males. The decrease in reproductive capacity was considered by the authors to be related partially to embryotoxicity (Morrissey *et al.*, 1988).

Developmental toxicity: IRC-JCL mice received a single intraperitoneal injection of 175, 200 or 225 mg/kg bw theophylline on day 12 of gestation. Subsequently, 40% of dams in the high-dose group died, and dyspnoea and convulsions were observed in those in the low- and mid-dose groups. Fetal body weight was decreased with the high and medium doses, and the incidence of resorptions was significantly increased with the high dose. Malformations were observed in all treated groups; these included cleft palate, digital defects and macrognathia. Subcutaneous haematomas were also seen (Fujii & Nishimura, 1969).

ICR mice received an intraperitoneal injection of 100, 150 or 200 mg/kg bw theophylline on one of gestation days 10-13. A dose-related increase in the incidence of resorptions and malformations — mostly cleft palate — was observed, with a peak embryotoxic response in fetuses treated on day 11 (Tucci & Skalko, 1978).

Sprague-Dawley rats were fed theophylline in the diet (average daily dose, 124, 218 or 259 mg/kg bw) on days 6-15 of gestation. In parallel, Swiss CD-1 mice received theophylline in the drinking-water (daily doses, 282, 372 or 396 mg/kg bw) on the same gestation days. Slight maternal toxicity (decreased weight gain) was observed in high-dose rats and in mid- and high-dose mice. In rats, fetal body weight was significantly decreased with the medium and high doses, and live litter size was decreased with the high dose; no malformation was observed. In mice, fetal body weight was significantly decreased in the mid- and high-dose groups, and the incidence of resorptions was increased in the mid-dose group (Lindström *et al.*, 1990).

(iv) *Genetic and related effects*

The genetic effects of theophylline have been reviewed (Timson, 1975). Additional information on theophylline is included in reviews by Timson (1977) and Tarka (1982).

The results described below are listed in Table 1 on p. 403, with the evaluation of the Working Group, as positive, negative or inconclusive, as defined in the footnotes. The results are tabulated separately for the presence and absence of an exogenous metabolic sytem. The lowest effective dose (LED), in the case of positive results, or the highest ineffective dose (HID), in the case of negative results, are shown, together with the appropriate reference. The studies are summarized briefly below.

As reported in an abstract, theophylline at 3.2 mM displaced 50% of intercalated acridine orange from DNA *in vitro* (Richardson *et al.*, 1981). In extracts of *Escherichia coli*, theophylline selectively inhibited some purine nucleoside phosphorylases (Koch & Lamont, 1956). In *E. coli*, which may not demethylate the drug, theophylline was not incorporated to 'any great extent' into DNA (Koch, 1956) and, unlike other inhibitors of DNA synthesis, had little or no effect on λ prophage induction (Noack & Klaus, 1972). The effects of theophylline on relevant targets other than DNA are discussed in the monograph on caffeine (p. 332).

Theophylline gave negative results in the *Bacillus subtilis rec* assay [details not given]. It was mutagenic to *E. coli* chemostat cultures (Novick & Szilard, 1951; Novick, 1956), and this activity could be inhibited by guanosine (Novick & Szilard, 1952). It was also mutagenic to *E. coli* and in the *B. subtilis* multigene sporulation test, but not to *Salmonella typhimurium*.

In *Saccharomyces cerevisiae*, theophylline promoted sporulation in glucose-containing medium, where it increased the intracellular cAMP level. It had no effect on DNA, RNA or protein synthesis or in medium in which glucose was replaced by potassium acetate (Tsuboi & Yanagishima, 1975).

Theophylline induced mutation in *Ophiostoma multiannulatum* and *Euglena gracilis*. It induced chromosomal fragment formation and translocations in *Allium cepa* root tips, but no chromosomal aberration in *Vicia faba* root tips.

Theophylline was reported in an abstract to induce aneuploidy in *Drosophila melanogaster* (Mittler & Mittler, 1968).

Doses of theophylline greater than 0.3 mg/ml inhibited DNA synthesis in mouse L5178Y lymphoma cells, LS929 mouse fibroblasts and V79 Chinese hamster cells. Theophylline slightly reduced the size of newly synthesized DNA in both unirradiated and ultraviolet-irradiated cells and reversibly inhibited the DNA gap-filling process in ultraviolet-damaged cells (Lehmann, 1973, abstract; Lehmann & Kirk-Bell, 1974). Theophylline also inhibited DNA synthesis in human

fibroblastoid EUE cells, and the shape of the dose-response curves and the absence of theophylline-induced DNA strand breaks indicated that theophylline does not directly damage the DNA but acts as a metabolic inhibitor (Slamenová *et al.*, 1986). The results of a study with synchronized HeLa S3 cells exposed to theophylline indicate that the block in DNA replication results from inhibition of histone 1 phosphorylation, which prevents the normal release of chromatin structure between G_1 and S phases (Dolby *et al.*, 1981).

The incidence of 6-thioguanine-resistant mutants in V79 cells was not increased by theophylline.

In the pseudodiploid Chinese hamster cell line, Don-6, theophylline induced a dose-related increase in sister chromatid exchange but did not induce micronuclei. It induced sister chromatid exchange in hamster lung fibroblasts *in vitro* [details not given]. The induction of sister chromatid exchange is not necessarily due to a directly damaging effect upon DNA, since theophylline can inhibit poly-(ADP-ribose)polymerase (Levi *et al.*, 1978). This activity is associated with the induction of sister chromatid exchange (Morgan & Cleaver, 1982) and may even give rise to false-positive effects, the primary effect upon DNA being due to bromodeoxyuridine (Natarajan *et al.*, 1981).

Theophylline induced sister chromatid exchange in human cells *in vitro*. Studies on the induction of chromosomal aberrations in human and mammalian cells is equivocal. The apparent lack of mutagenic activity of theophylline may be due to the antimitotic threshold being the same as the mutagenic threshold, so that any mutant cells produced are unable to reproduce (Timson, 1972).

Butcher and Sutherland (1962) reported that theophylline is the most potent naturally occurring phosphodiesterase inhibitor. Inhibition of cyclic 3′,5′-nucleotide phosphodiesterase from beef heart by theophylline is apparently competitive, with a K_i in the order of 0.1 mM. Since theophylline in combination with increasing concentrations of cAMP (up to 500 μg/ml) had no clastogenic effect, Weinstein *et al.* (1973) argued that inhibition of phosphodiesterase is not involved in clastogenicity in human lymphocytes in culture.

In Chinese hamster ovary CHO-R1 cells, theophylline reduced the expression of parameters associated with transformation, causing an increase in surface fibronectin, cell-substratum adhesive strength and anchorage dependence for growth and a reduction in cell population saturation density (Rajaraman & Faulkner, 1984).

Theophylline inhibited mitosis of mouse ear epidermal cells in the G_2 phase (Marks & Rebien, 1972). In the host-mediated assay with *S. typhimurium* (G46, nonsense mutation) in Swiss albino mice, theophylline gave negative results. It

Tale 1. Genetic and related effects of theophylline

Test system	Results		Dose LED/HID	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
BSD, Bacillus subtilis rec assay (spore)	-	-	0.0000	Kawachi et al. (1980)
SA0, Salmonella typhimurium TA100, reverse mutation	-	-	0.0000	Kawachi et al. (1980)
SA0, Salmonella typhimurium TA100, reverse mutation	-	-	0.0000	Ishidate et al. (1981)
SA0, Salmonella typhimurium TA100, reverse mutation	-	-	500.0000	Slameňová et al. (1986)
SA7, Salmonella typhimurium TA1537, reverse mutation	-	-	0.0000	Ishidate et al. (1981)
SA9, Salmonella typhimurium TA98, reverse mutation	-	-	0.0000	Kawachi et al. (1980)
SA9, Salmonella typhimurium TA98, reverse mutation	-	-	0.0000	Ishidate et al. (1981)
SA9, Salmonella typhimurium TA98, reverse mutation	-	-	500.0000	Slamenova et al. (1986)
ECR, Escherichia coli, phage T5-resistance	+	0	150.0000	Novick & Szilard (1951)
ECR, Escherichia coli Methionine auxotrophy to protrophy	+	0	500.0000	Greer (1958)
BSM, Bacillus subtilis, multigene sporulation test	+	0	7500.0000	Sacks & Mihara (1983)
???, Ophiostoma multiannulatum, ascomycete, auxotrophic mutations	+	0	0.0000	Fries & Kihlman (1948)
???, Euglena gracilis, auxotrophic mutations	+	0	0.0000	Come & Travis (1969)
???, Euglena gracilis, auxotrophic mutations	+	0	0.0000	Schiff et al. (1971)
ACC, Allium cepa, chromosomal aberrations	+	0	200.0000	Kihlman & Levan (1949)
VFC, Vicia faba, chromosomal aberrations	-	0	3600.0000	Kihlman & Sturelid (1975)
VFC, Vicia faba, chromosomal aberrations	-	0	900.0000	Kihlman & Sturelid (1975)
???, Silkworm, mutation	-	0	0.0000	Kawachi et al. (1980)
G9H, Gene mutation, Chinese hamster lung V79 cells, 6-thioguanine	-	-	9.0000	Slameňová et al. (1986)
SIA, Sister chromatid exchange, hamster lung fibroblasts	+	0	0.0000	Kawachi et al. (1980)
SIC, Sister chromatid exchange, Chinese hamster Don-6 cells	+	0	180.0000	Sasaki et al. (1980)
MIA, Micronucleus test, Chinese hamster Don-6 cells	-	0	900.0000	Sasaki et al. (1980)
CIA, Chromosomal aberrations, hamster lung fibroblasts	+	0	0.0000	Kawachi et al. (1980)
CIC, Chromosomal aberrations, Chinese hamster lung fibroblasts (CHL)	+	0	0.0000	Ishidate et al. (1981)
CIC, Chromosomal aberrations, Chinese hamster lung fibroblasts (CHL)	+	0	500.0000	Ishidate (1988)
CIC, Chromosomal aberrations, Chinese hamster lung fibroblasts (CHL)	-	-	2000.0000	Ishidate (1988)
SHF, Sister chromatid exchange, human embryo fibroblasts	+	0	0.0000	Kawachi et al. (1980)
SHF, Sister chromatid exchange, human diploid fibroblasts (HE2144)	+	0	180.0000	Sasaki et al. (1980)
MIH, Micronucleus test, human diploid fibroblasts (HE2144)	-	0	360.0000	Sasaki et al. (1980)
CHL, Chromosomal aberrations, human lymphocytes	+	0	500.0000	Weinstein et al. (1975)
CHL, Chromosomal aberrations, human lymphocytes	-	0	1800.0000	Timson (1972)
CHT, Chromosomal aberrations (chromatid breaks), HeLa cells	+	0	13000.0000	Ostertag (1966)
HMM, Host-mediated assay, Salmonella typhimurium in Swiss mice	-	0	0.0000	Gabridge & Legator (1969)
SVA, Sister chromatid exchanges, Chinese hamster bone-marrow	+	0	150.0000 i.p.	Renner (1982)
CBA, Chromosomal aberrations, rat bone-marrow	-	0	0.0000 oral	Kawachi et al. (1980)
DLM, Dominant lethal test, male Swiss CD-1 mice	-	0	380.0000 i.p.	Epstein & Shafer (1968)

i.p., intraperitoneal; oral, by gavage

induced sister chromatid exchange in Chinese hamsters, but did not cause chromosomal aberrations in rat bone marrow *in vivo* (Renner, 1982). Theophylline did not induce dominant lethal mutations in male Swiss CD-1 mice.

(*b*) *Humans*

(*i*) *Absorption, distribution, metabolism and excretion*

The metabolism and pharmacokinetics of theophylline in humans have been reviewed (Haley, 1983b; Mungall, 1983; Arnaud, 1984; Stavric, 1988).

Theophylline is readily absorbed after an oral dose. The absorbed fraction of a dose of 7.5 mg/kg bw averaged 99% (Hendeles *et al.*, 1977); however, the absorption of oral theophylline can be delayed by food (Welling *et al.*, 1975; Heimann *et al.*, 1982). Ageing had no effect on the rate or extent of absorption (Cusack *et al.*, 1980; Shin *et al.*, 1988). Peak serum levels are generally achieved within 1.5-2 h (Hendeles *et al.*, 1977; Ogilvie, 1978).

At 17 μg/ml, 56% of theophylline was bound reversibly to adult plasma proteins compared to ~36% in cord plasma proteins from full-term infants (Aranda *et al.*, 1976; Ogilvie, 1978). Protein binding was also reduced to 11-13% during the last two trimesters of pregnancy (Frederiksen *et al.*, 1986). Theophylline is not accumulated in specific target organs: it was distributed in erythrocytes (Ogilvie, 1978), saliva (Culig *et al.*, 1982) and breast milk (milk:serum concentration ratio, 0.70; Yurchak & Jusko, 1976), but not extensively in adipose tissue (Rohrbaugh *et al.*, 1982). Theophylline also passed into the amniotic fluid (Sommer *et al.*, 1975; Arwood *et al.*, 1979; Labovitz & Spector, 1982). The presence of a blood-brain barrier reduces theophylline concentrations in the brain, and a cerebrospinal fluid:plasma ratio of 0.68 was reported (Kadlec *et al.*, 1978).

The elimination half-time of theophylline was 15-60 h in premature infants for at least the first two to four weeks postpartum compared to 3.4 h in children aged one to four years (Aranda *et al.*, 1976), while the corresponding values for adults exhibited large variations, between 3 and 11 h (Jenne *et al.*, 1972; Hunt *et al.*, 1976; Chrzanowski *et al.*, 1977). Theophylline clearance increased by 10% per year over the age range 1-15 years (Driscoll *et al.*, 1989). In subjects over 60 years, half-times of 5.4-9.0 h were reported (Nielsen-Kudsk *et al.*, 1978; Fox *et al.*, 1983).

The half-times were decreased from 7 h in nonsmokers to 4 h in smokers, possibly due to induction of theophylline metabolizing enzymes (Jenne *et al.*, 1975; Hunt *et al.*, 1976). Use of oral contraceptives lowered total plasma clearance and prolonged the half-time of theophylline (9-10 h *versus* 6-7 h), with no change in plasma binding or volume of distribution (Tornatore *et al.*, 1982; Roberts *et al.*, 1983). Cirrhotic patients and patients with acute pulmonary oedema have a prolonged half-time of theophylline (between 23 and 26 h) and decreased plasma

clearance (Piafsky *et al.*, 1977a,b; Staib *et al.*, 1980). Plasma binding is also reduced in cirrhotic patients (37% *versus* 53% in normal subjects) (Piafsky *et al.*, 1977a). The half-time of theophylline was prolonged significantly during exercise (Schlaeffer *et al.*, 1984).

The apparent volumes of distribution of theophylline ranged from 0.44 to 0.51 l/kg bw in adults and children (Ogilvie, 1978), but a value of 0.69 was found in premature newborns (Aranda *et al.*, 1976). The distribution volume and elimination half-time of theophylline were increased in the third trimester of pregnancy (Frederiksen *et al.*, 1986).

Disproportionate increases and decreases in serum theophylline concentrations with changes in oral dosage in adults suggest that the rate of elimination is dose-dependent (Jenne *et al.*, 1972; Ogilvie, 1978; Tang-Liu *et al.*, 1982a). Several studies showed that linear pharmacokinetics is a valid model within the therapeutic range (Mungall *et al.*, 1982; Rovei *et al.*, 1982; Brown *et al.*, 1983). Dose-dependent pharmacokinetics seem to be more frequent in children and in some individual adult patients and are generally seen with plasma theophylline concentrations greater than 15 μg/ml (Weinberger & Ginchansky, 1977). Nonlinearity may be due to metabolic saturation or to the diuretic effect of theophylline (Lesko, 1979, 1986; Tang-Liu *et al.*, 1982b). There is also an age-dependent variation in the elimination of theophylline (Jusko *et al.*, 1979).

Experiments with human liver microsomes showed the involvement of at least two cytochrome P450 isozymes in the metabolism of theophylline (Robson *et al.*, 1988). The pathways were presented in Figure 1.

Only 7-12% of theophylline is excreted unchanged in the urine, while several parallel pathways produced 9-18% 3-methylxanthine, 0.3-4% 1-methylxanthine, traces of 3-methyluric acid, 13-26% 1-methyluric acid and the main metabolite, 1,3-dimethyluric acid, at 35-55% (Arnaud, 1984; Birkett *et al.*, 1985). Allopurinol, a xanthine oxidase inhibitor, increased 1-methylxanthine excretion and decreased 1-methyluric acid excretion, demonstrating that the conversion is mediated by xanthine oxidase (Grygiel *et al.*, 1979). Methylation of theophylline into caffeine is the predominant metabolic pathway in neonates because the other enzymatic systems are immature (Bory *et al.*, 1979). Methylation occurs to some extent in adults, but caffeine does not accumulate because it is metabolized further (Tang-Liu & Riegelman, 1981). Patients with decompensated liver cirrhosis have different patterns of urinary metabolites of theophylline than healthy subjects (Staib *et al.*, 1980).

Dietary factors have been shown to modify the elimination of theophylline in children (Feldman *et al.*, 1980) and adults (Anderson *et al.*, 1979). A high protein diet and diets containing charcoal-broiled beef resulted in accelerated elimination of theophylline (Kappas *et al.*, 1978; Feldman *et al.*, 1980). Serum theophylline levels

follow a circadian rhythm (for review, see Smolensky & McGovern, 1985), but these effects are less pronounced than interindividual variations (Straughn *et al.*, 1984).

Studies of twins demonstrated that the large interindividual variations in theophylline elimination observed in human subjects are predominantly under genetic control (Miller *et al.*, 1985).

(ii) *Toxic effects*

The toxicology of theophylline has been reviewed (Ellis, 1983; Haley, 1983a,b; Bukowskyj *et al.*, 1984; Stavric, 1988).

Toxicity can be produced easily owing to its narrow therapeutic index (Labovitz & Spector, 1982; Greenberg *et al.*, 1984; Singer & Kolischenko, 1985). A small percentage of patients taking theophylline therapeutically to control asthma may develop toxicity at serum levels of 20-30 μg/ml. These effects are generally not seen at levels below 15 μg/ml (Stavric, 1988).

Administration of theophylline to premature babies in the preterm period caused sleep disturbances that persisted after the drug had been cleared from the body (Thoman *et al.*, 1985). In a study on long-term effects of theophylline administration in the preterm period, no difference was found at one or two years of age as a function of drug treatment (Nelson *et al.*, 1980). The question of whether theophylline affects learning ability in children remains open (Stavric, 1988).

'Mild' toxicity may include headache, gastrointestinal disturbances, hypotension, irritability and insomnia. Symptoms of 'severe toxicity' include tachycardia, arrhythmia, cardiac arrest and serious neurological symptoms. Seizures and death have occurred (Helliwell & Berry, 1979; Winek *et al.*, 1980; Woo *et al.*, 1980; Woodcock *et al.*, 1983; Greenberg *et al.*, 1984; Singer & Kolischenko, 1985; Stavric, 1988).

Studies of a possible association between consumption of methylxanthines and benign breast disease are discussed on pp. 347-350.

(iii) *Effects on reproduction and prenatal toxicity*

No association was seen between use of bronchodilators (theophylline being one of 11 preparations used) and congenital abnormalities in the offspring (Nelson & Forfar, 1971). This finding was corroborated by a study of 117 women who had used the drug (Heinonen, 1982).

(iv) *Genetic and related effects*

Lymphocytes from a mother given continuous treatment for asthma with theophylline-containing drugs and from her stillborn triploid child both showed increased frequencies of chromatid breaks (14 and 16%, respectively; Halbrecht *et al.*, 1973). Timson (1975) suggested that theophylline may have been involved in the

induction of the chromatid breaks. [The Working Group noted that the medication also contained ephedrine, phenobarbital and diphenylhydramine.]

The apparent lack of mutagenic activity of theophylline and other methylxanthines in man may be due to the fact that the antimitotic threshold is the same as the mutagenic threshold, so that any mutant cells produced are unable to reproduce; the net effect is therefore nonmutagenicity (Timson, 1972).

3.3 Epidemiological studies of carcinogenicity to humans

Studies on methylxanthines are summarized in the monograph on caffeine.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Theophylline is found in black tea and to a lesser extent in green coffee, cocoa cotyledon and dried mate. Theophylline is synthesized on an industrial scale and is used principally in pharmaceutical preparations.

Per-caput daily intake of theophylline from black tea in the USA has been estimated to be 0.14 mg.

4.2 Experimental carcinogenicity data

No data on the carcinogenicity of theophylline were available.

In the one adequate study, theophylline applied to the skin of female mice induced a significantly smaller number of ultraviolet light-induced tumours than in controls.

4.3 Human carcinogenicity data

No data were available to the Working Group to evaluate the carcinogenicity of theophylline *per se*.

For descriptions of studies on methylxanthines, see the monograph on caffeine.

4.4 Other relevant data

Limited data on mothers taking theophylline during pregnancy showed no excess in the frequency of malformations in their offspring.

Theophylline given by gavage at high doses decreased testicular weight in rats and mice, but there was no change in semen characteristics. Administration of theophylline in the diet at dose levels that were mildly toxic to adults caused decreased numbers of litters per breeding pair, decreased live litter size, an increased number of resorptions and decreased neonatal weight. Abnormal sperm were observed in rats but not in mice at high dose levels.

Theophylline induced sister chromatid exchange in Chinese hamsters *in vivo* but did not induce dominant lethal mutations in mice or chromosomal aberrations in the bone marrow of rats. Theophylline gave negative results in a host-mediated assay with *Salmonella typhimurium* in mice. In cultured human cells, theophylline induced sister chromatid exchange and chromosomal breaks but not micronuclei or chromosomal aberrations. It induced sister chromatid exchange and chromosomal aberrations but not micronuclei or gene mutation in animal cells *in vitro*. Results on the induction of chromosomal aberrations in plants are equivocal. In lower eukaryotes, it induced gene mutations. Theophylline gave negative results in the *Salmonella*/mammalian microsome assay but induced mutation in other bacteria.

4.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity in humans of theophylline.

There is *inadequate evidence* for the carcinogenicity in experimental animals of theophylline.

Overall evaluation

Theophylline is *not classifiable as to its carcinogenicity to humans (Group 3).*

5. References

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[1]For description of the italicized terms, see Preamble, pp. 27-31.

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