SULFAMETHOXAZOLE

This substance was considered by previous working groups, in 1980 (IARC, 1980) and 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

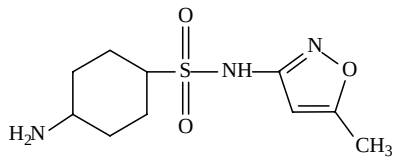
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 723-46-6
Deleted CAS Reg. No.: 129378-89-8
Chem. Abstr. Name: 4-Amino-*N*-(5-methyl-3-isoxazolyl)benzenesulfonamide
IUPAC Systematic Name: N^1-(5-Methyl-3-isoxazolyl)sulfanilamide
Synonyms: 3-(*para*-Aminophenylsulfonamido)-5-methylisoxazole; 5-methyl-3-sulfanilamidoisoxazole; sulfamethylisoxazole; sulfamethoxazol; 3-sulfanilamido-5-methylisoxazole; sulfisomezole; sulphamethoxazole

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{10}H_{11}N_3O_3S$ Relative molecular mass: 253.28

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White to slightly off-white crystalline powder (Gennaro, 1995)
(*b*) *Melting-point*: 167 °C (Budavari, 2000)

(*c*) *Spectroscopy data*: Infrared [prism/grating (80313)], ultraviolet (46353), nuclear magnetic resonance [proton (53244), C-13 (32650)] and mass spectral data have been reported (Rudy & Senkowski, 1973; Sadtler Research Laboratories, 1995; Lide & Milne, 1996).

(*d*) *Solubility*: Slightly soluble in water (0.5 g/L) and benzene; slightly soluble in chloroform, diethyl ether and isopropanol; soluble in ethanol and methanol (Rudy & Senkowski, 1973; Gennaro, 1995)

1.1.4 *Technical products and impurities*

Sulfamethoxazole is available as 500-mg and 1-g tablets and as a 500-mg/5 mL oral suspension (Gennaro, 1995).

Trade names for sulfamethoxazole include Gantanol, MS-53, Radonil, Ro 4-2130 and Sinomin.

1.1.5 *Analysis*

Several international pharmacopoeias specify infrared and ultraviolet absorption spectrophotometry with comparison to standards as the methods for identifying sulfamethoxazole; potentiometric or electrometric titration with sodium nitrite is used to assay its purity. In pharmaceutical preparations, sulfamethoxazole is identified by infrared absorption spectrophotometry and thin-layer chromatography; visible absorption spectrophotometry and potentiometric or electrometric titration with sodium nitrite are used to assay for sulfamethoxazole content (British Pharmacopoeia Commission, 1993; Society of Japanese Pharmacopoeia, 1996; US Pharmacopeial Convention, 1999).

Methods for the analysis of sulfamethoxazole in human and animal fluids (milk, plasma, serum, urine) and tissues (muscle, organs), eggs, bee honey, meat-based baby food, animal wastewater, effluents and river water and drugs have been reported. The methods include enzyme immunoassay, gas chromatography with atomic emission, flame ionization or nitrogen–phosphorus detection, gas chromatography with mass spectrometry or pulsed positive ion–negative ion–chemical ionization mass spectrometry, thin-layer chromatography, high-performance thin-layer chromatography, liquid chromatography with fluorescence or fluorimetric detection, high-performance liquid chromatography (HPLC) with electrospray tandem mass spectrometry, fluorescence, photodiode array, spectrofluorimetric, or ultraviolet detection, and reversed-phase HPLC with ultraviolet detection (Ascalone, 1978; Schlatterer & Weise, 1982; Petz, 1983; Siegert, 1985; Van der Steuijt & Sonneveld, 1987; Aerts *et al.*, 1988; Van Poucke *et al.*, 1989; Kruzik *et al.*, 1990; Rychener *et al.*, 1990; Takatsuki & Kikuchi, 1990; Diserens *et al.*, 1991; Mineo *et al.*, 1992; Nie *et al.*, 1992; Takeda & Akiyama, 1992; Guggisberg *et al.*, 1993; Martin *et al.*, 1993; Mengelers *et al.*, 1993; Mooser & Koch, 1993; Shao *et al.*, 1993; Tsai & Kondo, 1993; Endoh *et al.*, 1994; Horie *et al.*, 1994; Tachibana *et al.*, 1994; Takahashi *et al.*, 1994; Lin *et al.*, 1995; Tsai & Kondo, 1995a,b; Nishimura *et al.*,

1996; Edder *et al.*, 1997; Gehring *et al.*, 1997; Le Boulaire *et al.*, 1997; Chiavarino *et al.*, 1998; Jen *et al*., 1998; Petkov & Gechev, 1998; Hirsch *et al*., 1999; Stoev & Michailova, 2000).

1.2 Production

Sulfamethoxazole can be prepared by reacting 3-amino-5-methylisoxazole with *para*-acetamidobenzenesulfonyl chloride (made by treating acetanilide with chlorosulfonic acid). The acetyl group is then cleaved to yield sulfamethoxazole (Rudy & Senkowski, 1973; Gennaro, 1995).

Information available in 2000 indicated that sulfamethoxazole was manufactured by 29 companies in China, 26 companies in India, three companies each in Brazil and Turkey, two companies in Taiwan and 1 company each in Croatia, Egypt, Hungary, Israel, Japan, Mexico, the Republic of Korea, Spain, Switzerland and the USA (CIS Information Services, 2000a).

Information available in 2000 indicated that sulfamethoxazole was formulated as a pharmaceutical by 194 companies in India, 41 companies in Brazil, 38 companies in Mexico, 29 companies in Germany, 26 companies in Spain, 24 in the Philippines, 20 companies in Argentina, 19 companies in South Africa, 18 in China, 17 in Indonesia, 15 companies in Colombia, 14 companies in Turkey, 13 companies each in Ecuador, Peru, Switzerland and the USA, 12 companies in Taiwan, 11 companies in Chile, 10 companies in Italy, 9 each in Greece and Thailand, eight companies in the Islamic Republic of Iran, seven companies each in Austria, Singapore and the United Kingdom (sodium salt), six companies each in Canada, Japan, Malaysia and the Netherlands, five companies each in Egypt, Poland and Portugal, four companies each in Australia, France and Viet Nam, three companies each in Belgium, Israel, the United Kingdom and Venezuela, two companies each in Bulgaria, Sri Lanka, Sweden, Hong Kong, Hungary and Ireland and one company each in Denmark, Ireland, Latvia, Malta, New Zealand, Pakistan, the Republic of Korea, the Russian Federation, Saudi Arabia, the Slovak Republic and Yugoslavia (CIS Information Services, 2000b).

1.3 Use

Sulfamethoxazole is an antibacterial drug which has been used since the 1960s in the treatment of various systemic infections in humans and other species. The main use has been in the treatment of acute urinary tract infections. It has also been used against gonorrhoea, meningitis and serious respiratory tract infections (*Pneumocystis carinii*) and prophylactically against susceptible meningococci. Despite its relatively unfavourable pattern of tissue distribution, it is the sulfonamide most commonly used around the world in combination with trimethoprim or pyrimethamine for the treatment of various systemic infections. The combination with trimethoprim is used mainly for the treatment of urinary tract infections; with pyrimethamine, it is used in the treatment

of chloroquine-resistant *Plasmodium falciparum* malaria (IARC, 1980; Gennaro, 1995; Budavari, 2000).

The usual adult oral dose of sulfamethoxazole is initially 2 g, followed by 1 g twice a day. The usual paediatric (> 1 month of age) oral dose is initially 50–60 mg/kg bw, followed by 25–30 mg/kg bw every 12 h; the total dose should not exceed 75 mg/kg bw per day (Gennaro, 1995).

1.4 Occurrence

1.4.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 2000), about 21 200 workers, including 11 500 nurses, 4200 pharmacists, 2100 health aides and 1500 veterinarians, were potentially exposed to sulfamethoxazole in the USA.

1.4.2 *Environmental occurrence*

No data were available to the Working Group.

1.5 Regulations and guidelines

Sulfamethoxazole is listed in the pharmacopoeias of China, the Czech Republic, European, France, Germany, Italy, Japan, Poland, the United Kingdom and the USA and in the European and International pharmacopoeias (Royal Pharmaceutical Society of Great Britain, 2000; Society of Japanese Pharmacopoeia, 1996; Swiss Pharmaceutical Society, 1999; US Pharmacopeial Convention, 1999; Vidal, 2000). It is registered for human use in Finland, Ireland, the Netherlands, Norway, Portugal, Spain and Sweden (Instituto Nacional de Farmacia e do Medicamento, 2000; Irish Medicines Board, 2000; Medical Products Agency, 2000; Medicines Evaluation Board Agency, 2000; National Agency for Medicines, 2000; Norwegian Medicinal Depot, 2000; Spanish Medicines Agency, 2000).

2. Studies of Cancer in Humans

Sulfamethoxazole was included in a hypothesis-generating cohort study designed to screen a large number (215) of drugs for possible carcinogenicity, which covered more than 140 000 subscribers enrolled between July 1969 and August 1973 in a prepaid medical care programme in northern California (USA). Computer records of persons to whom at least one drug prescription has been dispensed were linked to the cancer records of hospitals covered by the medical care programme and the regional cancer

registry. The observed numbers of cancers were compared with those expected, standardized for age and sex, for the entire cohort. Three publications summarized the findings for follow-up periods of up to 7 years (Friedman & Ury, 1980), 9 years (Friedman & Ury, 1983) and 15 years (Selby *et al*., 1989). In the 7-year report, among the 1709 persons who had used sulfamethoxazole, significant excesses were noted of nasopharyngeal cancer (three cases observed versus 0.1 expected; $p < 0.002$) and of cervical cancer after a 2-year lag time allowance (seven cases observed versus 2.2 expected; $p < 0.05$), while a significant deficit of colon cancers was reported (no cases observed versus 4.7 expected; $p < 0.05$). No changes in the significance of the observed associations was noted in the 9-year follow-up report. In the 15-year follow-up report, positive associations with *p* values between 0.01 and 0.05 were observed for cancers of the lung (23 observed versus 14.5 expected), uterine cervix (12 observed versus 5.9 expected), multiple myeloma (five observed versus 1.3 expected) and lymphomas and leukaemias combined (16 observed versus 7.6 expected). [The Working Group noted, as did the authors, that, since some 12 000 comparisons were made in this hypothesis-generating study, the associations should be verified independently. Data on duration of use were not provided.]

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Rat: Groups of 25–26 male and 24–25 female Charles River CD rats [age unspecified] were fed diets providing a dose of 0 (control), 25, 50, 150, 300 or 600 mg/kg bw per day sulfamethoxazole for 60 weeks, at which time the animals were killed. Thyroid follicular-cell tumours were observed in 0/28, 7/30, 20/29, 19/27, 23/23 treated males and females combined, at the five doses, respectively. No thyroid tumours were observed in two control groups of 28 and 26 rats. Lung metastases were observed in four rats at the three higher doses (Swarm *et al*., 1973). [The Working Group interpreted the tumours as adenomas and carcinomas from illustrations in the report.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and Its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The acetylation pattern of sulfamethoxazole was examined in six male and 16 female healthy volunteers selected according to their acetylation phenotype by analysis

of the acetylation pattern of sulfadimidine. They were given a single oral dose of 10 mg/kg bw sulfamethoxazole, and blood (at 6 h) and urine (0–6 h) were analysed for the presence of total and free sulfamethoxazole (total minus free was considered to be the acetylated form). Sulfamethoxazole did not appear to undergo polymorphic acetylation (Bozkurt *et al.*, 1990).

Acetylation of sulfamethoxazole by human hepatic monomorphic (NAT1) and polymorphic (NAT2) arylamine *N*-acetyltransferase showed a higher affinity for the monomorphic enzyme (K_{max}, 1.2 mmol/L and approximately 5 mmol/L for NAT1 and NAT2, respectively). The higher affinity for NAT1 indicated that acetylation by this enzyme predominates at therapeutic plasma concentrations, in agreement with the observed monomorphic acetylation of sulfamethoxazole *in vivo* (Cribb *et al.*, 1993). There were no differences in affinity between human recombinant NAT1 and NAT2 enzymes in converting sulfamethoxazole hydroxylamine to the reactive *N*-acetoxysulfamethoxazole (Nakamura *et al.*, 1995).

Sulfamethoxazole was oxidized to its hydroxylamine metabolite in an NADPH-dependent process by liver microsomes prepared from two human livers. Three healthy volunteers ingested 1000 mg of sulfamethoxazole, and their urine was collected for 24 h. Sulfamethoxazole hydroxylamine constituted 3.1 ± 0.7% of the drug excreted in the urine, and 54% of the ingested dose was excreted during the same period (Cribb & Spielberg, 1992). In four male and two female volunteers given a single dose of 800 mg of sulfamethoxazole, 16.5 ± 5.5% was recovered as the parent compound, 46.2 ± 6.6% as N^4-acetylsulfamethoxazole and 2.4 ± 0.8% as the hydroxylamine in the urine after 96 h. The mean residence time of the hydroxylamine metabolite was 5.5 ± 1.5 h, and its renal clearance time was 4.4 ± 0.9 h (Van der Ven *et al.*, 1994).

4.1.2 *Experimental systems*

An oral dose of 1.0 g/kg bw sulfamethoxazole was absorbed rapidly by mice, and a peak plasma concentration of approximately 1.0 mg/mL was achieved 1 h after administration. The plasma elimination half-time was approximately 6 h. In rats, high concentrations of sulfamethoxazole were found in kidney, lung, liver, spleen and brain. The rate of elimination of the drug from these tissues paralleled that from blood (Nishimura *et al.*, 1958).

Murine hepatic microsomes oxidized sulfamethoxazole at the N^4-position to form the hydroxylamine in a cytochrome P450-catalysed reaction (Cribb & Spielberg, 1990).

4.1.3 *Comparison of animals and humans*

Sulfamethoxazole did not show evidence of polymorphic acetylation in humans. Both mice and humans oxidized sulfamethoxazole to the potentially toxic hydroxylamine metabolite.

4.2 Toxic effects

4.2.1 *Humans*

Sulfamethoxazole is associated with a variety of idiosyncratic toxic effects, including hepatotoxicity and systemic hypersensitivity reactions (reviewed by Mandell & Petri, 1996). Of hospitalized patients who were monitored during 359 courses of therapy with sulfamethoxazole, 3.0% experienced allergic reactions. Skin rashes, eosinophilia and drug fever were the commonest manifestations, and serious reactions were rare (Koch-Weser *et al*,. 1971).

Human monocytes and neutrophils activated by phorbol myristate acetate *in vitro* metabolized sulfamethoxazole to its hydroxylamine and to nitrosulfamethoxazole, whereas the presumed nitroso intermediate was not detected (Cribb *et al.*, 1990). Purification of human peripheral blood mononuclear cells showed that the $CD8^+$ population was highly susceptible to the cytotoxic effects of sulfamethoxazole hydroxylamine (Hess *et al.*, 1999). Covalent binding of sulfamethoxazole to human liver microsomal protein was NADPH-dependent. The pattern of protein targets was similar in human and rat liver microsomes (Cribb *et al.*, 1996).

In two separate double-blind cross-over studies with human volunteers, one with 10 men and the other one with 10 women, half the subjects were given co-trimoxazole (80 mg trimethoprim and 400 mg sulfamethoxazole per tablet) as two tablets daily for 10 days and, after 3 weeks, co-trifamole (80 mg trimethoprim and 400 mg sulfamoxole per tablet) as two tablets immediately, then one tablet twice a day for 10 days. The remaining volunteers received these treatments in reverse order. Administration of co-trimoxazole resulted in a significant but moderate lowering of serum concentrations of thyroxine and triiodothyronine and of the free thyroxine index, whereas the serum thyroid-stimulating hormone (TSH) concentrations were not altered (Cohen *et al.*, 1980).

The plasma concentrations of thyroxine, triiodothyronine and TSH were measured in 49 subjects, six of whom were boys aged 2–19 years, who had received co-trimoxazole (10 mg sulfamethoxazole and 2 mg trimethoprim per kg bw per day) for up to 11 years (mean, 4.7 years). All the TSH values were within the normal range. An analysis of variance showed no significant difference in mean thyroxine or triiodothyronine concentrations with duration of prophylaxis or the age of the patients (Smellie *et al.*, 1982).

4.2.2 *Experimental systems*

Rat liver microsomes activated sulfamethoxazole *in vitro* to products that covalently bound to microsomal protein in the presence of NADPH, as detected by a polyclonal antibody. Sulfamethoxazole and sulfamethoxazole hydroxylamine elicited similar patterns of covalent binding targets. No covalent binding was detected *in vivo* after administration of sulfamethoxazole to rats (Cribb *et al.*, 1996).

Sulfamethoxazole hydroxylamine, but not sulfamethoxazole, was toxic to the immortal rat thyroid cell line FRTL5, which lacks active thyroid peroxidase. Both sulfamethoxazole and sulfamethoxazole hydroxylamine were toxic to primary sheep thyroid cells with active thyroid peroxidase (Gupta *et al.*, 1992).

Groups of four male Wistar rats were given a weekly intraperitoneal injection of 10, 50 or 250 mg/kg bw sulfamethoxazole, 10 mg/kg bw sulfamethoxazole hydroxylamine, 10 mg/kg bw nitroso sulfamethoxazole or vehicle, for 4 weeks. The immunogenic potential of sulfamethoxazole and its reactive metabolites was assessed by analysing serum samples from these rats for the presence of anti-sulfamethoxazole immunoglobulin G antibodies. A high titre of antibodies was present in sera from rats given nitroso sulfamethoxazole, whereas no antibodies were detected in sulfamethoxazole-treated or control rats. Sulfamethoxazole hydroxylamine resulted in only a weak immunogenic response after 3 weeks of dosing (Gill *et al.*, 1997).

Groups of 10 male and 10 female Sprague-Dawley rats were given 25 mg/kg bw sulfamethoxazole by gavage daily for 10 consecutive days. There was no clear indication that sulfamethoxazole had altered thyroid hormone synthesis, even though the serum TSH concentration was significantly elevated in male rats. When sulfamethoxazole was administered with trimethoprim (co-trimoxazole) at 600 mg/kg bw per day for 10 days, marked changes in hormone concentrations consistent with altered thyroid hormone homeostasis were produced. Significant increases in thyroid gland weight and follicular-cell hyperplasia were also demonstrated (Cohen *et al.*, 1981). [The Working Group noted that this dose was equivalent to the lowest dose used in the bioassay of carcinogenicity.]

Groups of 25 male and 25 female CD rats were given diets containing sulfamethoxazole at concentrations providing an intake of 0, 25, 50, 150, 300 or 600 mg/kg bw per day for up to 60 weeks. Autopsies and histological examinations were performed on five rats per sex per group at the end of 13 and 52 weeks and on all surviving animals at the end of the experiment. At 13, 52 and 60 weeks, dose-dependent increases in the weights of the thyroid glands were observed, and dose-dependent thyroid hyperplasia was seen in all treated animals. In groups of four male and four female rhesus monkeys given sulfamethoxazole by gavage at a dose of 0, 50, 150 or 300 mg/kg bw per day on 6 days per week for 52 weeks, no thyroid hyperplasia was observed (Swarm *et al.*, 1973).

In a comparison of species differences in the anti-thyroid effects of the sulfonamide prototype drug sulfamonomethoxine, groups of six to seven male Sprague-Dawley rats were given an oral dose of 30 or 270 mg/kg bw per day, while groups of three to four male squirrel monkeys (*Saimiri sciureus*) were given an oral dose of 270 mg/kg bw per day through the nose for 5 weeks. Rats at the highest dose showed a decrease in serum thyroxine concentration and in ^{131}I incorporation into thyroid hormone precursors, with an increased serum concentration of TSH, increased thyroid weight and hyperplasia of the follicular epithelium of the thyroid gland. No change was found in monkey thyroids. The concentration of sulfamonomethoxine required for 50% inhibition *in vitro*

of peroxidase isolated from rat thyroid was 2.2×10^{-7} mol/L. For the enzyme isolated from monkey thyroid this value was $> 10^{-4}$ mol/L (Takayama *et al.*, 1986).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

Although sulfamethoxazole can be used alone, it is usually administered in the form of co-trimoxazole, a combination with the folic acid antagonist trimethoprim.

Sulfamethoxazole crossed the human placenta and reached a peak concentration at 10 h. After several gestational weeks, the concentration of sulfamethoxazole was lower in amniotic fluid and in the fetus than in maternal serum (Reid *et al*., 1975). No increase in the incidence of defects was found in the offspring of 120 pregnant women who had been treated with sulfamethoxazole for bacteriuria, but only 10 of the women had been treated before the 16th week of pregnancy (Williams *et al.*, 1969). Heinonen *et al*. (1977) reported no increase in the rate of malformations in the offspring of 46 women treated with sulfamethoxazole during the first four lunar months of pregnancy.

In a case–control study in Hungary of use of co-trimoxazole during 1980–84, 1.25% (124/9893) of mothers of healthy babies had used co-trimoxazole compared with 2.31% (144/6228) ($p < 0.001$) of mothers of babies with congenital anomalies. Most of the mothers had used the drug during the third trimester of pregnancy, however, and analysis of the association between exposure during the critical periods and a range of nine specific malformations showed no increased risk in the exposed group. Nevertheless, the total rate of malformations was significantly raised (odds ratio, 2.3; 95% confidence interval, 1.2–4.0), and a teratogenic risk cannot be excluded (Czeizel, 1990). [The Working Group noted that the contribution of trimethoprim cannot be assessed.]

4.3.2 *Experimental systems*

Sulfamethoxazole given daily at 600 mg/kg bw on days 8–16 of gestation to Wistar rats caused cleft palate in the fetuses (Udall, 1969). It had no adverse effect on fetal development of rabbits (Medical Economics Co., 2000).

4.4 Effects on enzyme induction or inhibition and gene expression

No data were available to the Working Group.

4.5 Genetic and related effects

4.5.1 *Humans*

Administration to patients of sulfamethoxazole in combination with trimethoprim at therapeutic doses (800 mg sulfamethoxazole and 80 mg trimethoprim twice a day

for 10 days) did not increase the frequency of chromosomal aberrations in peripheral lymphocytes (Stevenson *et al*., 1973) or in bone-marrow (Sørensen & Krogh Jensen, 1981). However, an increased number of micronuclei was observed in the bone marrow (Sørensen & Krogh Jensen, 1981).

4.5.2 *Experimental systems* (see Table 1 for references)

Sulfamethoxazole did not induce mutations in *Salmonella typhimurium.* [The Working Group noted that the bacterial toxicity of the compound limited the doses that could be used.] No chromosomal aberrations were observed in human lymphocytes treated with sulfamethoxazole *in vitro*.

Sulfamethoxazole in combination with trimethoprim (250 μg/mL) did not increase the frequency of chromosomal breaks in human fibroblasts *in vitro* (Byarugaba *et al*., 1975).

4.6 Mechanistic considerations

Insufficient data were available to evaluate the genotoxicity of sulfamethoxazole.

Sulfamethoxazole induced thyroid enlargement and hyperplasia in rats but not in monkeys. It was toxic to thyroid cells *in vitro* in the presence but not in the absence of thyroid peroxidase. There is no clear evidence that sulfamethoxazole alters thyroid homeostasis in rats. A prototype sulfonamide, sulfamonomethoxine, acted as an anti-thyroid substance in rats, but not in monkeys. Sulfamethoxazole is metabolized to a hydroxylamine metabolite in both humans and experimental animals.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Sulfamethoxazole is a sulfonamide drug. It is used worldwide in the treatment of bacterial and protozoal infections, particularly in combination with other drugs in treating acute urinary tract infections and malaria.

5.2 Human carcinogenicity data

In one hypothesis-seeking epidemiological study, statistically significant positive associations were noted between sulfamethoxazole use and the risks for cancers of the lung and cervix and multiple myeloma and the combination of lymphomas and leukaemias.

Table 1. Genetic and related effects of sulfamethoxazole

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	10 µg/plate	Mortelmans *et al.* (1986)
Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	150 µg/mL	Stevenson *et al.* (1973)

[a] –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose

5.3 Animal carcinogenicity data

Sulfamethoxazole was tested by oral administration in one study in rats. It produced follicular-cell adenomas and carcinomas of the thyroid.

5.4 Other relevant data

Sulfamethoxazole does not appear to be polymorphically acetylated in humans. Sulfamethoxazole is metabolized to its potentially toxic hydroxylamine in both humans and experimental animals. This metabolite has been associated with idiosyncratic toxicity, such as systemic hypersensitivity reactions, in humans. Sulfamethoxazole induced thyroid enlargement and hyperplasia in rats but not in monkeys. There is no convincing evidence that sulfamethoxazole alters thyroid hormone homeostasis in rats.

Administration of sulfamethoxazole to patients at therapeutic doses in combination with trimethoprim increased the number of micronuclei in their bone-marrow cells but did not increase the frequency of chromosomal aberrations. Sulfamethoxazole did not induce chromosomal aberrations in human lymphocytes *in vitro* or mutations in bacteria. Insufficient data were available to reach a conclusion about the genotoxicity of the agent.

5.5 Evaluation

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

There is *limited evidence* in experimental animals for the carcinogenicity of sulfamethoxazole.

Overall evaluation

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

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