CIMETIDINE

1. Chemical and Physical Data

Cimetidine

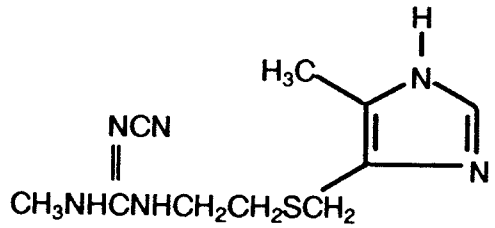
1.1 Synonyms

Chem. Abstr. Services Reg. No.: 51481-61-9

Chem. Abstr. Name: Guanidine *N*-cyano-*N'*-methyl-*N''*-(2-{[(5-methyl-1*H*-imidazol-4-yl)methyl]thio}ethyl)-

Synonym: 2-Cyano-1-methyl-3-[2-(5-methylimidazo-4-ylmethylthio)ethyl]guanidine

1.2 Structural and molecular formula and molecular weight



$C_{10}H_{16}N_6S$ Mol. wt: 252.34

1.3 Chemical and physical properties of the pure substance

From Windholz (1983) and Bavin *et al.* (1984)

(*a*) *Description*: White to off-white crystalline powder

(*b*) *Melting point*: 141-143°C (base), 193°C dec (hydrochloride)

(*c*) *Solubility*: Soluble (1.14%) in water at 37°C; soluble in ethanol; very slightly soluble in chloroform; insoluble in diethyl ether. The hydrochloride is freely soluble in water; soluble in ethanol; very slightly soluble in chloroform; and practically insoluble in diethyl ether.

(*d*) *Spectroscopy data*: Ultraviolet, infrared, nuclear magnetic resonance and mass spectral data have been reported.

(*e*) *Stability*: Dry compound, stored in a closed container at room temperature, showed no decomposition after five years. Cimetidine hydrochloride is stable for 48 h at normal room temperature when diluted with most commonly used solutions for intravenous injection.

1.4 Technical products and impurities

Trade names: Acibilin; Aciloc; Acinil; Altramet; Cianosel; 'Cim'; Cimal; Cimegan; Cimet; Cimetid; Cimetidina; Cimetin; Cimetum; Cinamet; Cinulcus; Citimid; Citius; Climatidine; Dina; Duncamet; Duogastril; Duractin; Dyspamet; Edalene; Etidine; Eureceptor; Evicer; Fisiol; Fremet; Gasmetin; Gastrobitan; Gastro H2; Gastromet; Himetin; Itacem; Lucimet; Lucomet; Mansal; Nimus (Udine) Gadol; Notul; Novocimetine; Peptol; Prometidine; Regastric; SKF 92334; Stomakon; Tagacid; Tagama; Tagagel; Tagamet; Tametin; Temic; Tratul; Tratul Retard (SR); Ulcedine; Ulcenon; Ulcerdine; Ulcerfen; Ulcestop; Ulcidin; Ulcimet; Ulcodina; Ulcomedina; Ulhys; Vagolisal; Valmagen

Hydrochloride: Biomag; Brumetidina; Cimet; Notul

Cimetidine is available for oral administration as 200- or 300-mg tablets. The hydrochloride is available for oral administration as a 300 mg/5 ml solution and for parenteral administration as a 150 mg/ml liquid.

Impurities in tablets available in the USA include cellulose, D&C yellow #0, FD&C Blue #2, FD&C Red #40, FD&C yellow #6, hydroxypropyl methylcellulose, iron oxides (see IARC, 1987a), magnesium stearate, povidone, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, starch and titanium dioxide (see IARC, 1989a). Impurities in the liquid (oral) preparation are ethanol (2.8%), FD&C Yellow #6, methylparaben, polyoxyethylene polyoxypropylene glycol, propylene glycol, propylparaben, saccharin sodium (see IARC, 1987b), sodium chloride, sodium phosphate, sorbitol and water. Solutions for intramuscular or intravenous injections contain phenol (0.5%; see IARC, 1989b) (Barnhart, 1989).

Single-dose, premixed plastic containers for intravenous administration are available (300 mg cimetidine, 0.45 g sodium chloride and no preservative) (Barnhart, 1989).

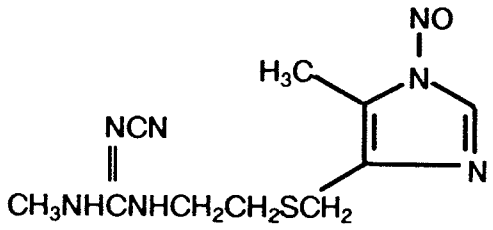
N-*Nitrosocimetidine*

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 73785-50-7

Chem. Abstr. Name: Guanidine, *N*-cyano-*N'*-methyl-*N''*-nitroso-*N'''*-(2-{[(5-methyl-1*H*-imidazol-4-yl)methyl]thio}ethyl)-

1.2 Structural and molecular formulae and molecular weight



$C_{10}H_{15}N_7OS$ Mol wt: 281.33

1.3 Chemical and physical properties of the pure substance

From Bavin *et al.* (1980) and Foster *et al.* (1980)

(*a*) *Description*: Pale-yellow crystals

(*b*) *Melting-point*: 112-113°C

(*c*) *Solubility*: Soluble in dimethylsulfoxide

(*d*) *Spectroscopy data*: Ultraviolet, nuclear magnetic resonance and field desorption mass spectra have been recorded.

(*e*) *Stability*: Unstable in alkaline solution

1.4 Technical products and impurities

N-Nitrosocimetidine has been synthesized for research purposes (Bavin *et al.*, 1980; Foster *et al.*, 1980). The *N*-methyl-*N'*-cyanoguanidine moiety of cimetidine can be converted to the corresponding *N*-nitroso derivative (*N*-nitrosocimetidine) by the action of acidic solutions of nitrite (Bavin *et al.*, 1980).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Cimetidine is prepared from 2-methyl-3-hydroxymethyl-1*H*-imidazole *via* a multistep synthesis involving sequential additions of 2-mercaptoethylamine, dimethylcyanodithioimidocarbonate and methylamine and variations of this method (Durant *et al.*, 1974; Bavin *et al.*, 1984). The hydrochloride is prepared by addition of hydrochloric acid and ethyl acetate as an ethanolic suspension of cimetidine (Bavin *et al.*, 1984).

Cimetidine is synthesized in Brazil, Hungary, India, Italy, Mexico, the Republic of Korea, Spain, Taiwan and Yugoslavia (Chemical Information Services, 1989-90).

In Sweden, cimetidine sales in 1988 were 2.32 defined daily doses (1 g) per 1000 inhabitants (Apoteksbolaget, 1988, 1989). In Finland, cimetidine sales in 1987 were 0.15 defined daily doses per 1000 inhabitants (Finnish Committee on Drug Information and Statistics, 1987). In the USA, cimetidine was the sixth ranking prescription drug in 1988 (La Piana Simonsen, 1989).

Cimetidine is not known to occur as a natural product.

The intragastric formation of *N*-nitrosocimetidine has been proposed *via* reaction of cimetidine with nitrous acid (Elder *et al.*, 1979a,b).

2.2 Use

As a histamine H_2-receptor antagonist, cimetidine inhibits gastric acid secretion and reduces pepsin output; it may also inhibit other actions of histamine that are mediated *via* H_2-receptors. Its clinical indications include duodenal and gastric ulcers, oesophageal reflux, selected cases of persistent dyspepsia and pathological hypersecretory states such as the Zollinger-Ellison syndrome. Due to its capacity to inhibit acid secretion, it is also indicated for the prophylaxis of gastrointestinal haemorrhage in stress ulceration and in patients at risk of acid aspiration during general anaesthesia. Cimetidine may also be used to reduce malabsorption and fluid loss in patients with the short-bowel syndrome and to reduce the degradation of enzyme supplements given to patients with pancreatic insufficiency (Reynolds, 1989). Treatment of damage to the gastric mucosa by non-steroidal anti-inflammatory drugs (Friedman *et al.*, 1989) is a minor indication.

Cimetidine may be given orally (400 mg two to four times daily), by the nasogastric route or parenterally by intramuscular or slow intravenous injections (200 mg) as well as by intravenous infusion (400 mg in 1 h repeated every 4-6 h) (Reynolds, 1989). In maintenance therapy of duodenal ulcer, cimetidine has been administered daily for up to five years (Barnhart, 1989).

The use of cimetidine in children, in particular in neonates, is limited. In full-term neonates, the dosage adjustments are based on renal function, and the dose of 15-20 mg/kg daily is reduced in premature infants (Ziemniak *et al.* 1984). The dosage regimen in children aged 4-13 years is 30 mg/kg bw daily, divided into three or more doses (see Reynolds, 1989).

In elderly people, the standard dose of cimetidine can be reduced by about 30-50% without loss of effectiveness (see p. 248) (Redolfi *et al.*, 1979).

2.3 Analysis

Analysis of cimetidine and its metabolites in biological fluids by high-performance liquid chromatography has been described (Randolph *et al.*, 1977; Kunitani *et al.*, 1981; Ziemniak *et al.*, 1981; Lloyd & Martin, 1985; Chiou *et al.*,

1986; Kaneniwa *et al.*, 1986; Strong & Spino, 1987; Rustum & Hoffman, 1988). Cimetidine can be analysed in pharmaceutical preparations by high-performance liquid chromatography, thin-layer chromatography and spectrophotometric methods (Bavin *et al.*, 1984; Lovering & Curran, 1985).

A method for the analysis of *N*-nitrosocimetidine in human gastric juice samples using reverse-phase high-performance liquid chromatography with an *N*-nitroso compound specific detector has been reported (Shuker & Tannenbaum, 1983).

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

3.1 Carcinogenicity studies in animals

Cimetidine

(*a*) *Oral administration*

Mouse: In a two-generation carcinogenicity study, groups of male BALB/c and female C57Bl/6 mice [numbers unspecified], seven to eight weeks of age, were given pharmaceutical-grade cimetidine at either what was stated to be a common human dose—0.113 mg/ml—or at 1.13 mg/ml in their drinking-water for two weeks. Treated mice were mated, and F_0 females were treated throughout gestation, lactation and the remainder of their lives. The hybrid progeny (F_1) were weaned at four weeks and were also dosed throughout their life. A group of 20 untreated female C57Bl/6 mice served as controls for the treated dams and were mated with untreated BALB/c males. A group of 51 male and 66 female untreated hybrid progeny served as controls for the F_1 generation. The average daily doses of cimetidine were 18.8 mg/kg bw and 190 mg/kg bw, and the average total doses were 15.5 g/kg bw and 155 g/kg bw in the low-dose and high-dose groups, respectively. All moribund mice were killed and subjected to complete necropsy, and all major organs, tissues and lesions were examined histologically. Among the treated C57Bl/6 dams, the effective numbers of animals were 15 at the low dose and 16 at the high dose, with mean survival times of 21-24 months; no significant difference in either survival rates or tumour incidence was observed in comparison with the control group. Among the progeny, the effective numbers of females ranged from 39 to 66 among the different groups, with mean survival times of 28.0-30.8 months; the effective numbers of males ranged from 50 to 79 among the different groups, with mean survival times of 23.5-27 months. In the cimetidine-treated progeny, a significant dose-related increase in the incidence of lymphoid neoplasms [site and

histology unspecified] was observed in females (31/66, 30/65 and 41/59 in the control, low- and high-dose groups, respectively; $p = 0.008$, Fisher's exact test) (Anderson *et al.*, 1985). [The Working Group noted the high incidence of this neoplasm in control animals.]

Rat: Groups of 65, 70 and 100 male and 65, 70 and 99 female SPF Wistar rats, 5.5 weeks of age, received clinical-grade cimetidine at 150, 378 or 950 mg/kg bw (which represent 30, 75 and 190 times the dose required for 50% inhibition of basal gastric acid secretion in the rat and are equivalent to 9, 22.6 and 57 times the recommended daily dose for a 60-kg human) in distilled water by gavage daily for two years. One control group of 84 males and 85 females received distilled water by gavage daily, and another group of 107 males and 108 females served as untreated controls. Interim kills were carried out at 6, 10 and 12 months after the start of the experiment, during which a total of 54/235 and 55/234 treated males and females and 32/191 and 32/193 control males and females were killed. The experiment was terminated at 105-106 weeks, at which time survival was: males—untreated controls, 58/107; water controls, 34/84; low-dose, 24/65; mid-dose, 14/70; and high-dose, 34/100; females—untreated controls, 71/108; water controls, 32/85; low-dose, 26/65; mid-dose, 18/70; and high-dose, 34/99. During the first year of the experiment, those rats that died did so mainly as a result of either reflux or direct administration of the dose into the trachea. All rats were necropsied, and major organs and tissues were examined histologically. An increased incidence of benign Leydig-cell tumours of the testis was observed among treated animals (low-dose, 15/65; mid-dose, 14/68; high-dose, 23/98) as compared to combined controls (35/191). The increase was significant in the low- and high-dose groups ($p < 0.025$ for both groups; Peto test: Peto *et al.*, 1980). A slightly greater incidence of follicular-cell tumours (benign and malignant) of the thyroid gland was observed in high-dose males (4/98) as compared to control males (2/191) ($p = 0.049$, Peto exact test) (Leslie *et al.*, 1981).

Dog: Eight male and four female beagle dogs, 7-9.5 months of age, received a daily oral administration of cimetidine in film-coated tablets at 144 mg/kg bw for 385 weeks. Four male and two female controls received placebo tablets. Multiple biopsies of gastric mucosa were taken at intervals of about six months from week 177 to week 363. Two cimetidine-treated and three control dogs died during the experiment. All animals were necropsied, and numerous samples from the stomach and other major organs and tissues were examined histologically. No increase in the incidence of either neoplasms or preneoplastic lesions was observed among the treated animals (Walker *et al.*, 1987a). [The Working Group noted the small number of animals used and the high mortality].

(*b*) *Administration with other compounds*

Mouse: In the study described on p. 239, groups of male BALB/c and female C57Bl/6 mice were given sodium nitrite at either 0.184 or 1.84 mg/ml or cimetidine at 0.113 or 1.13 mg/ml with sodium nitrite at either 0.184 or 1.84 mg/ml in the drinking-water for two weeks. Treated mice were mated, and females were treated throughout gestation, lactation and for the remainder of their lives. The hybrid progeny were weaned at four weeks of age and dosed from that time throughout their lives. No increase in tumour incidence was seen in the dams. Among the progeny, there was a dose-related increase in the incidence of lung tumours in males: 30/52, 36/50 and 71/79 in the untreated control, low- and high-dose groups, respectively ($p < 0.01$, Cox exact test for trend) (Anderson *et al.*, 1985).

Rat: Two groups of 20 male Sprague-Dawley rats, weighing 250 g, were wounded surgically in the antro-fundic gastric mucosa. Seven days later, the groups received 1-1.4 ml of either sodium nitrate at 3.75 mg/ml and sodium nitrite at 0.75 mg/ml in deionized water (nitrate-nitrite solution) or commercial-grade cimetidine at 25 mg/kg bw in nitrate-nitrite solution, by gavage daily on six days per week for six months. A group of 50 males served as untreated controls. An interim kill of five rats from each group was carried out at six months, and all surviving rats were killed at 14-15 months. Including the five animals per group from the interim kill, 19 and 20 animals from the nitrate-nitrite and treated groups were necropsied, but samples for histological examination were taken only from the stomach and grossly visible lesions. No neoplasm was found (Elder *et al.*, 1982). [The Working Group noted the small number of animals used, the short duration of the study and the limited histological examination.]

Two groups of 25 Sprague-Dawley rats received weekly subcutaneous injections of either 1,2-dimethylhydrazine alone at 20 mg/kg bw for 16 weeks or concurrently with cimetidine at 100 mg/kg bw daily in the drinking-water for 26 weeks, at which time the experiment was terminated. One group of ten rats received cimetidine treatment only. No increase in the incidence of colonic tumours was observed in the combined cimetidine plus 1,2-dimethylhydrazine-treated group (15/22) over that in the group receiving 1,2-dimethylhydrazine alone (14/22); no such tumour occurred in rats given cimetidine alone (Nee *et al.*, 1984). [The Working Group noted the small number of animals used and the short duration of treatment.]

Two groups of 15 weanling male Sprague-Dawley rats received 1,2-dimethylhydrazine at 30 mg/kg bw in saline by gavage once a week for five weeks. Four days after the last treatment, the groups received either cimetidine at 500 mg/ml in the drinking-water or drinking-water alone, until the animals were killed, seven months after the beginning of the experiment. All animals were necropsied, and samples from the gastrointestinal tract and lymph nodes from the peritoneal cavity and

lungs were examined histologically. The incidence of colonic carcinomas among survivors was significantly different ($p < 0.05$; Mann-Whitney non-parametric test) for the group receiving 1,2-dimethylhydrazine (4/13) compared with that receiving 1,2-dimethylhydrazine and cimetidine together (10/14) (Caignard *et al.*, 1984). [The Working Group noted the absence of a group treated with cimetidine only.]

N-*Nitrosocimetidine*

Because of the suspicion that *N*-nitrosocimetidine might be a carcinogenic derivative of cimetidine, it was tested in a number of studies. *N*-Nitroso compounds are often potent carcinogens, and so, in these studies, small numbers of animals were used. Since the studies would have detected a potent carcinogen, they are included to support the interpretation that *N*-nitrosocimetidine is, at least, not a strong carcinogen.

(*a*) *Oral administration*

Mouse: In the study described on p. 239, groups of male BALB/c and female C57Bl/6 mice were given *N*-nitrosocimetidine (purity, 98%) at either 0.113 or 1.13 mg/ml in the drinking-water for two weeks. Treated mice were mated, and females were treated throughout gestation, lactation and for the remainder of their lives. The hybrid progeny were weaned at four weeks of age and dosed from that time throughout their life. The average daily doses of *N*-nitrosocimetidine were 18.8 mg/kg bw and 190.0 mg/kg bw, and the average total doses were 15.5 g/kg bw and 155 g/kg bw in the low-dose and high-dose groups, respectively. No significant difference in either survival rates or the incidence of tumours was observed between treated and control groups (Anderson *et al.*, 1985).

Two groups of 20 female hybrid B6D2F$_1$ mice, eight weeks of age, were given four weekly intragastric administrations of olive oil, which was used as the vehicle for other compounds; one week after the last dose, they received either *N*-nitrosocimetidine at 1.13 mg/ml in the drinking-water or deionized water alone. All survivors were killed 14 months after the beginning of treatment. Papillomas of the forestomach occurred in 2/20 mice receiving *N*-nitrosocimetidine and in 0/19 controls (Anderson *et al.*, 1988). [The Working Group noted the small number of animals used.]

Groups of male BALB/CanNCr mice, six weeks of age, received intraperitoneal injections of saline solution once a week for ten weeks, after which time they were given *N*-nitrosocimetidine at 0, 1.0 or 1.8 mg/ml in the drinking-water. All survivors were killed at 14 months. The effective numbers of animals were 13 in the group receiving *N*-nitrosocimetidine and 15 in the control group. Lung neoplasms [type unspecified] were observed in 3/13 animals in each treated group and in 6/15

control mice (Anderson *et al.*, 1988). [The Working Group noted the small number of animals used and the short duration of the study.]

Rat: Groups of 20 male and 20 female outbred Sprague-Dawley rats, approximately 100 days old, received *N*-nitrosocimetidine at 50 or 500 mg/kg bw by gavage twice a week for one year. A group of 50 male and 50 female rats served as untreated controls. All animals were observed for life or were killed when moribund, and were necropsied. Samples from the forestomach, glandular stomach, duodenum and all other organs with gross lesions were examined histologically. Mean survival was 393 days in high-dose animals, 400 days in low-dose animals and 630 days in controls. No increase in the incidence of tumours and no gastric neoplasm were found in treated animals (Habs *et al.*, 1982a,b). [The Working Group noted the small number of animals used and the poor survival of treated animals.]

Two groups of 20 male Sprague-Dawley rats, weighing 250 g, were wounded surgically in the antro-fundic gastric mucosa. Seven days later, the groups received 1-1.4 ml of either sodium nitrate at 3.75 mg/ml and sodium nitrite at 0.75 mg/ml in deonized water (nitrate-nitrite solution) or *N*-nitrosocimetidine at 2.80 mg/ml in nitrate-nitrite solution, by gavage daily on six days per week for six months. A group of 50 males served as untreated controls. An interim kill of five rats from each group was carried out at six months, and all surviving rats were killed at 14-15 months. Including the five animals per group from the interim kill, 19, 16 and 9 animals from the respective groups were necropsied, but samples for histological examination were taken only from the stomach and grossly visible lesions. A gastric carcinoma at the site of wounding was found in one rat treated with *N*-nitrosocimetidine. No other neoplasm was found (Elder *et al.*, 1982). [The Working Group noted the small number of animals used.]

Groups of 20 male and 20 female Fischer 344 rats [age unspecified] received *N*-nitrosocimetidine at 20 ml (0.15 mg/ml) in deionized water daily as drinking fluid on five days per week for 106 weeks (total dose, 1.6 g/rat). Groups of 20 males and 20 females were untreated and served as controls. All survivors were killed at week 131, and all animals were necropsied and major organs and lesions examined histologically. At 90 weeks, survival was 19/20 males and 20/20 females in the treated group and 15/20 males and 17/20 females in controls. No increase in the incidence of tumours was observed (Lijinksy & Reuber, 1984). [The Working Group noted the small number of animals used.]

(*b*) *Skin application*

Mouse: Groups of 20 female Swiss mice [age unspecified] received twice-weekly 25-µl skin applications on the shaved interscapular skin of either *N*-nitrosocimetidine (reagent grade) at 2.2 or 5.6 mg/ml in acetone (total doses, 12 or

31 mg/mouse), or acetone alone for 110 weeks or were left untreated. Skin was the only tissue examined grossly and histologically. At week 100, survival among treated animals was 18/20 at the low dose and 13/20 at the high dose. A malignant lymphoma of the skin [site unspecified] was observed in one high-dose mouse (Lijinsky, 1982). [The Working Group noted that the tumour incidence among control groups was not specified and that survival was poor in the group given the high dose.]

3.2 Other relevant data

(*a*) *Experimental systems*

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

The kinetics, absorption, distribution, metabolism and elimination of cimetidine in humans and experimental animals have been reviewed (Griffiths *et al.*, 1977).

In rats and dogs, cimetidine is rapidly absorbed; the concentration of unchanged cimetidine in plasma is greater than that of any metabolite, and the plasma half-time is about 1 h. The drug is excreted mainly unchanged in the urine. The principal metabolite in both rats and dogs is formed by oxidation of the side-chain sulfur to give the sulfoxide (Taylor, D.C. *et al.*, 1978).

In rats, detoxication of *N*-nitrosocimetidine involves denitrosation, primarily (but not exclusively) by haemoglobin sulfhydryl residues. The rates of degradation of *N*-nitrosocimetidine by isolated whole blood decreased in the order: rat > mouse $\approx$ guinea-pig > hamster $\approx$ human; the half-time of *N*-nitrosocimetidine at 37°C was ~2 min in hamster blood and 27 min in human blood. After intravenous administration to hamsters *in vivo*, the half-time of *N*-nitrosocimetidine was $\leq$5 min and degradation *via* denitrosation reached 100%. Additional denitrosating activity was found in the cytosol of several organs from rats and hamsters; this activity required reduced glutathione (Jensen, 1983; Jensen *et al.*, 1987).

The metabolic fate of *N*-nitrosocimetidine has been investigated, although it has not been shown to be formed in animals *in vivo*.

Radiolabelled *N*-nitrosocimetidine, but not cimetidine, methylated DNA in a variety of tissues in rats after oral administration (Gombar & Magee, 1982). In studies in which cimetidine was administered with an excess of nitrite by stomach tube to rats, no evidence could be obtained for the presence of O^6-methylguanine in DNA isolated from stomach, liver or intestine (large and small pooled) (Kyrtopoulos *et al.*, 1982). *N*-Nitrosocimetidine produced a low level of DNA alkylation (determined as 7-methylguanine) in the liver and other organs of hamsters after intravenous administration (Jensen *et al.*, 1987).

(ii) *Toxic effects*

The oral LD_{50}s of cimetidine were approximately 2.6 g/kg bw in mice, 5 g/kg bw in rats, 4 g/kg bw in hamsters and 2.60 g/kg bw in dogs. The intraperitoneal LD_{50}s were 470 mg/kg bw in mice, 650 mg/kg bw in rats and 880 mg/kg bw in hamsters (Crean *et al.*, 1981).

Daily oral administration of 160 mg/kg bw cimetidine to female Sprague-Dawley rats for two months increased total gastrin-cell numbers, gastrin-cell density of antral mucosa and parietal-cell density of fundic mucosa, as compared with controls (Del Tacca *et al.*, 1987). In contrast, in male Wistar/Lewis rats receiving cimetidine orally at 150-200 mg/kg bw daily for up to 12 months, it was not possible to demonstrate by autoradiography epithelial proliferation in either fundus or antrum as a consequence of treatment (Eastwood & Quimby, 1983).

In studies of up to 24 months' duration, rats receiving repeated doses of cimetidine at up to 950 mg/kg bw per day showed few adverse effects. Liver weight was consistently increased at the highest dose, and testis, prostate and seminal vesicle weights were reduced in a dose- and time-related manner (Brimblecombe *et al.*, 1985).

In a study of up to 12 months' duration, two dogs receiving cimetidine at 504 mg/kg bw per day orally exhibited degenerative changes in the liver, renal tubular nephrosis and elevated levels of serum transaminases. No such change was seen with doses of 366 mg/kg bw per day or less. Prostate weights were reduced in a dose- and time-related manner. In beagle dogs administered cimetidine at 144 mg/kg bw per day orally, no treatment-related effect was seen after four years, on the basis of haematology, clinical biochemistry, urinalysis, electrocardiography or clinical condition, and no treatment-associated change was observed in biopsies of gastric mucosa. After seven years of follow-up, no change of the stomach mucosa was seen during regular biopsy (Crean *et al.*, 1981; Brimblecombe *et al.*, 1985).

In-vivo and in-vitro studies suggest that cimetidine inhibits gastric acid secretion in rats and dogs by blocking histamine H_2-receptors in the gastric mucosa (Brimblecombe *et al.*, 1978). Cimetidine administered intraperitoneally to male Wistar rats at 20 mg/kg bw twice daily for seven days reduced the gastric mucosal concentrations of prostaglandin E_2 and 6-keto-prostaglandin F_{1a}, both 30 min and 24 h after the last injection (Arakawa *et al.*, 1988).

In rats, the oral LD_{50} of *N*-nitrosocimetidine did not differ from that of cimetidine itself. No tissue-specific toxic lesion could be attributed to the nitroso derivative (Ogiu *et al.*, 1986).

(iii) *Effects on reproduction and prenatal toxicity*

In routine safety evaluation studies on cimetidine, including fertility and peri- and postnatal studies in rats and teratology studies in mice, rats and rabbits, no

adverse effect was reported with oral doses of up to 950 mg/kg bw (Brimblecombe *et al.*, 1978). [The Working Group noted the lack of detailed reporting.]

Cimetidine has been shown to possess weak antiandrogenic activity in rats, as shown by reduced weights of testis, prostate and seminal vesicles (Brimblecombe *et al.*, 1978; Pereira, 1987). Inhibition of dihydrotestosterone binding to the prostatic androgen receptor has been demonstrated (Sivelle *et al.*, 1982).

Differentiation of the genital organs of male fetuses is influenced by endogenous testosterone produced during prenatal development, and gonadal and sexual dysfunction have been reported in adult male rats after prenatal and neonatal exposure to cimetidine at daily doses of 17.1 and 137 mg/kg bw in drinking-water from day 12 of pregnancy until weaning on postnatal day 21 (Anand & Van Thiel, 1982; Parker *et al.*, 1984a,b). These results were not confirmed in other studies. Rats were administered cimetidine at 180 mg/kg bw daily in the drinking-water from day 12 of pregnancy until the end of lactation or during late lactation only, or a combination of drinking-water during pregnancy and early lactation and gavage treatment during late lactation. Several end-points, such as anogenital distance, serum testosterone, mating performance and sexual organ weights, were evaluated soon after littering or up to 148 days postnatally. Maternally administered cimetidine had no effect in male offspring on any parameter measured (Walker *et al.*, 1987b).

In another study, cimetidine was administered to rats in drinking-water from day 17 of gestation through day 7 of lactation. With the highest drug concentration tested (4 mg/ml), the daily dose ingested ranged from about 400 mg/kg bw before parturition to approximately 850 mg/kg bw afterwards. The developmental profile of serum dehydroepiandrosterone, androstenedione, testosterone and 5-α-dihydrotestosterone, when measured at 1, 4 and 18 weeks of age, was unaffected by perinatal exposure to cimetidine (Shapiro *et al.*, 1988).

The effects of maternally administered cimetidine during lactation on the development of drug metabolizing enzymes in BALB/c mouse pups have been investigated. When dams were administered cimetidine at 50 mg/kg bw per day intraperitoneally for six weeks after delivery, microsomal enzyme activity was inhibited in pups. Dams were less affected than pups (Kwanashie, 1989).

(iv) *Genetic and related effects*

Cimetidine did not induce differential toxicity in *Escherichia coli* (Pool *et al.*, 1979; De Flora, 1981).

Cimetidine was reported not to be mutagenic to *Salmonella typhimurium* (De Flora & Picciotto, 1980; O'Connor *et al.*, 1987). Cimetidine alone or in combination with sodium nitrite gave negative results in *S. typhimurium* in a host-mediated assay in mice (Baumeister, 1982).

No single-strand breakage, measured by the alkaline elution assay, was found in the DNA of a transformed mouse epithelial cell line after treatment with cimetidine at concentrations of up to 5 mM (Schwarz *et al.*, 1980). In an alkaline elution assay with rat primary hepatocytes, the highest concentration of cimetidine hydrochloride (3 mM) induced a significant increase in the frequency of DNA strand breaks (Martelli *et al.*, 1983). No such effect was observed in human hepatocytes (Martelli *et al.*, 1986).

Cimetidine hydrochloride induced unscheduled DNA synthesis in cultures of rat primary hepatocytes (Martelli *et al.*, 1983; Lefevre & Ashby, 1985), while the base was inactive (Lefevre & Ashby, 1985). In another study, cimetidine [form not specified] did not induce unscheduled DNA synthesis in rat hepatocytes (Williams *et al.*, 1989). Human hepatocytes from four donors did not exhibit unscheduled DNA synthesis after treatment with cimetidine hydrochloride (Martelli *et al.*, 1986). In an abstract, it was reported that cimetidine did not induce mutation to 6-thioguanine resistance, to trifluorothymidine resistance or to ouabain resistance in a human lymphoblastoid cell line (TK6) after 1-h treatment with concentrations of up to 1.2 mM, with a cell survival of 6% (Tatsumi *et al.*, 1987).

Cimetidine did not induce sister chromatid exchange in human lymphocytes *in vitro* (Inoue *et al.*, 1985).

When rats were given cimetidine orally at 250 mg/kg bw, no DNA damage was detected in cells of the gastric mucosa (Pino & Robbiano, 1983) or in liver cells (Brambilla *et al.*, 1982); combination treatment with sodium nitrite also gave negative results.

N-Nitrosocimetidine and cimetidine treated with sodium nitrite in an acid environment like that of human gastric juice have consistently been shown to be directly mutagenic *in vitro*: either treatment induced differential toxicity and mutation in bacteria, inhibited DNA synthesis in human cells and induced DNA single-strand breaks, mutation, sister chromatid exchange, chromosomal damage and morphological transformation in mammalian cells. For a comprehensive tabulation of these data and their references, see Appendix 2.

(*b*) *Humans*

(i) *Pharmacokinetics*

The pharmacokinetics of cimetidine have been reviewed (Reynolds, 1989).

Cimetidine is readily absorbed from the gastrointestinal tract, and peak plasma concentrations are obtained about 1 h after administration on an empty stomach and about 2 h after administration with food (Somogyi & Gugler, 1983). The bioavailability of cimetidine is 60-70%, as a result of moderate first-pass metabolism. Twenty percent of cimetidine is bound to plasma proteins, and its elimination half-time from plasma is about 2 h; it is partially metabolized in the liver

to the sulfoxide and to hydroxymethylcimetidine. After intravenous administration, 50-80% of the dose was excreted unchanged in the urine. After an oral dose, the corresponding figure was 40%. Cimetidine penetrates the blood-brain barrier with difficulty but easily crosses the placental barrier and is excreted into milk, where the concentrations may be higher than those in plasma. Dose-dependent kinetics of cimetidine have been observed in neonates (Lloyd *et al.*, 1985).

A markedly reduced plasma clearance of cimetidine has been reported in elderly patients (Gugler & Somogyi, 1979; Redolfi *et al.*, 1979). A decrease in non-renal clearance of cimetidine was reported in patients with liver cirrhosis (Gugler *et al.*, 1982; Cello & Oie, 1983); in one study, this effect was limited to cirrhosis patients with a history of hepatic encephalopathy (Ziemniak *et al.*, 1983). Renal failure may lead to elevated plasma levels of cimetidine (Larsson *et al.*, 1982).

(ii) *Adverse effects*

The toxicity of cimetidine has been reviewed (Penston & Wormsley, 1986). Adverse effects are infrequent and are usually reversible following reduction of dosage or withdrawal of therapy. Diarrhoea, rashes and other allergic phenomena have been reported. Various symptoms of the central nervous system have been reported frequently, particularly at greater than therapeutic doses (Nelson, 1977; Illingworth & Jarvie, 1979; Schentag *et al.*, 1979). Adverse haematological effects possibly associated with cimetidine are rare and include granulocytopenia or agranulocytosis, thrombocytopenia and pancytopenia (Penston & Wormsley, 1986).

Strongly reduced gastric acid secretion favours colonization of the stomach by bacteria, some of which can reduce nitrate to nitrite and catalyse nitrosation of amino precursors at neutral pH (Hill, 1986; Leaf *et al.*, 1989). Since these conditions could lead to intragastric formation of nitroso compounds, gastric juice samples from patients before and after treatment with cimetidine have been analysed for total nitroso compounds or nitrite in several studies. Fasting gastric juice from 140 patients taking cimetidine for a variety of gastric or duodenal disorders (daily doses of 0.2-1.6 g for periods of one week to 45 months) and 267 subjects who had not taken the drug were analysed. Significantly higher mean levels of total nitroso compounds were found in the former group (Reed *et al.*, 1981).

In a study of a group of 23 peptic ulcer patients after a six-week course of 1 g cimetidine per day, a statistically significant increase in nitrite and nitroso compound concentrations was found (Stockbrugger *et al.*, 1982). In six volunteers who took 200 mg cimetidine three times a day and 400 mg a night for at least three weeks, increases in the level of gastric juice nitrite were found only rarely (Muscroft *et al.*, 1981). In eight healthy subjects studied half-hourly or hourly for 24-h periods before, during and after cimetidine treatment (two weeks with 1 g per day), no

significant difference in the level of intragastric nitrite or total nitroso compounds was found following cimetidine treatment (Milton-Thompson *et al.*, 1982).

Gastric juice and urine collected from 17 duodenal ulcer patients receiving 0.8 g cimetidine per day for four to six weeks were analysed for nitrosation capacity before, during and after treatment using the *N*-nitrosoproline test (Ohshima & Bartsch, 1981). Cimetidine treatment did not lead to a uniform or pronounced rise in gastric levels of total nitroso compounds or urinary *N*-nitrosoproline levels (Bartsch *et al.*, 1984).

The methods used for determining total nitroso compounds in gastric juice in all these studies have been criticized because of their lack of specificity (Pignatelli *et al.*, 1987); moreover, in none of the studies was *N*-nitrosocimetidine itself measured in the gastric juice samples.

Cimetidine inhibits cytochrome P450-dependent microsomal mixed-funciton oxidase (Pelkonen & Puuronen, 1980), elevating the plasma levels of other drugs, such as lignocaine, phenytoin, theophylline, warfarin and ciclosporin (Somogyi & Muirhead, 1987; Rodighiero, 1989).

(iii) *Effects on reproduction and prenatal toxicity*

A number of case reports have been published of cimetidine use in pregnancy, indicating no adverse effect (Corazza *et al.*, 1982; Meggs *et al.*, 1984) or abnormal outcome (Glade *et al.*, 1980; Say *et al.*, 1985); the significance of these reports cannot be assessed.

In a UK postmarketing surveillance study, 9928 patients given cimetidine in general practices were compared with 9351 age- and sex-matched unexposed people from the same practices; 98.8% of takers and 97.7% of controls were successfully followed up for at least one year (Colin-Jones *et al.*, 1983, 1985a,b). In the 20 exposed women and the 22 controls who became pregnant during the study year, there was no evidence of an adverse effect of cimetidine treatment.

Impotence, reduced sperm count and gynaecomastia have been reported in men treated with cimetidine. In one study, gynaecomastia was reported in 20/6240 men (3.2/1000), but in only 13 of these was cimetidine thought to be the likely cause. Impotence was reported in 12/6240 men (2/1000) taking cimetidine and in 3/5868 controls (0.5/1000); however, impotence and gynaecomastia were not reported in the same individuals (Colin-Jones *et al.*, 1985a,b). [The Working Group considered that, because of the method of ascertainment, underreporting was likely.] In other studies in which cimetidine was administered at doses larger than those normally used in ulcer therapy, these adverse effects were more common. In a study by Jensen *et al.* (1983), of patients with gastric hypersecretion (mostly Zollinger-Ellison syndrome) who were treated with high doses of cimetidine, 11/22 subjects developed one or more signs or symptoms of impotence, breast tenderness or

gynaecomastia. The 11 affected subjects had received a mean daily dose of 5.3 g, compared with 3.0 g in the unaffected group. Spence and Celestin (1979), however, reported gynaecomastia in 5/25 (20%) male patients treated with 1.6 g cimetidine daily. In all the reported cases, the condition reversed rapidly after cessation of and sometimes during treatment.

Several well-controlled studies have shown no effect of cimetidine on sperm count (Wang *et al.*, 1982; Paulsen *et al.*, 1983; Bianchi Porro *et al.*, 1985), but one showed a small but significant reduction (Van Thiel *et al.*, 1979). No consistent effect on plasma levels of gonadotrophins or sex hormones was demonstrated in these studies.

(iv) *Genetic and related effects*

When gastric juice from patients who had received cimetidine at 200 mg 2 h earlier was incubated with sodium nitrite at 10 μg/ml, a significant increase in the number of revertants was seen in *S. typhimurium* TA100 in the absence of an exogenous metabolic system (DeFlora & Picciotto, 1980).

Gastric juice taken from 49 patients 1-3 h after intake of cimetidine at 400 mg was mutagenic when tested in *S. typhimurium* TA100; no mutagenic activity was seen in samples taken 12 h later (Morris *et al.*, 1984). When the mutagenicity of gastric juice from eight fasting patients under cimetidine treatment (400 mg twice daily) was tested before and after administration of the drug, using *S. typhimurium* TA98 and TA100, considerable variation in mutagenicity was seen between subjects, all samples being mutagenic even before therapy. No significant change in mutagenic activity was detected after therapy and there was no relation to duration of therapy, changes in gastric pH or ulcer healing (O'Connor *et al.*, 1987)

3.3 Case reports and epidemiological studies in humans

(*a*) *Case reports*

Numerous case reports of neoplasms following cimetidine use have been published (Welsh *et al.*, 1977; Murray *et al.*, 1978; Taylor, T.V. *et al.*, 1978; Buck *et al.*, 1979; Elder *et al.*, 1979a,b; Reed *et al.*, 1979; Taylor *et al.*, 1979; Hawker *et al.*, 1980; Kjærgaard *et al.*, 1980; Knigge *et al.*, 1980; Stoddard *et al.*, 1980; Scotcher *et al.*, 1981; Taylor *et al.*, 1981; Kaplinsky *et al.*, 1982; Eschar *et al.*, 1983; Porter *et al.*, 1984; Stockley & Kiff, 1987). The stomach has been the most frequently reported cancer site, followed by lymphomas of the gastrointestinal tract; less commonly, benign and malignant tumours at other sites have been reported (Kaplinsky *et al.*, 1982; Eschar *et al.*, 1983). Most of the cases were diagnosed within one year; the longest interval was five years (Stockley & Kiff, 1987). In certain of the reports, gastric carcinoma had arisen after oesophagitis or duodenal ulcer—conditions not thought to be associated with gastric carcinoma. In other reports, gastric ulcers diagnosed

as benign on the basis of biopsy samples and appearance on gastroscopy have been followed by malignant changes.

(*b*) *Cohort studies*

A cohort of (initially) 9940 individuals who received cimetidine during 1977-79 in the UK and who were followed up for four years has been the subject of four papers (Colin-Jones *et al.*, 1982, 1983, 1985a,b). Also studied were (initially) 9366 controls matched for age, sex and general practice, who did not receive cimetidine, but these were followed up for only one year. For this reason, national rates were used as the standard for evaluation of mortality (incident cancers were evaluated only in the first year). A total of 330 deaths were due to neoplasms in cimetidine users (compared to 65.6 expected), most of the excess being gastric and lung cancers. The relative risks (RRs) declined markedly over the study period: for gastric cancer, the approximative RRs for men and women combined (and observed numbers) were 12.9 (45 deaths), 3.4 (12), 1.8 (6) and 2.3 (8) after one, two, three and four years follow-up, respectively. Some of the patients were known to have had cancer before cimetidine use was started, and, even among deaths after the first year, there were three such deaths from gastric cancer. For lung cancer, the RRs in the four periods were 2.8 (35 deaths), 2.0 (25), 1.4 (17) and 1.8 (22). In an approximately 5% sample of study participants, 45% of the exposed and 28% of unexposed subjects had smoked > 15 cigarettes per day five years previously. [The Working Group noted that cigarette smoking is associated with peptic ulcer as well as lung cancer and that smoking habits were not accounted for in the evaluation of lung cancer risk.]

A second cohort study concerned cancer incidence among 16 739 patients treated with cimetidine in Denmark in the period 1977-81 who were followed for up to eight years by linkage procedures with the central population and national cancer registers (Møller *et al.*, 1989). A total of 105 cases of gastric cancer were recorded, compared with 39.5 expected (RR, 2.6). The RR was greatest early in the follow-up period, declining markedly later. For sites with positive associations and for all other sites combined, the RRs and observed numbers of cases during the first year, during the second and third years and for more than three years of follow-up are shown in Table 1. The increased risks for gastric cancer were greater in persons with a diagnosis of gastric ulcer (19.3 (45 observed cases), 3.5 (16) and 3.2 (13) for the three time periods) than in those with duodenal ulcer (2.2, 1.1 and 1.1, with seven observed cases each). Increased incidences of gastric and certain other gastrointestinal malignancies were noted particularly in the first year of follow-up. The increased incidences of lymphatic and haematopoietic malignancies were due mainly to non-Hodgkin's lymphoma of the stomach and small intestine. The risk

Table 1. Relative risks (RRs) and numbers of cases observed after different periods in patients treated with cimetidine[a]

Site	< 1 year		1–3 years		> 3 years	
	RR	Obs	RR	Obs	RR	Obs
Stomach	9.4	57	2.3	27	1.7	21
Pancreas	4.7	21	1.5	15	1.7	14
Colon	2.1	23	1.8	38	1.3	26
Small intestine	10.5	4	3.9	3	3.4	2
Lymphatic and haematopoietic tissue	3.0	22	0.9	13	1.5	20
Lung	1.4	34	1.7	83	1.6	73
Other sites	1.1	91	1.4	218	1.1	169

[a]From Møller *et al.* (1989). RRs calculated by the Working Group for the two sexes combined

for lung cancer did not change appreciably over time. [The Working Group noted that no data on smoking status were provided.]

By record linkage, 3802 cimetidine users and an equal number of non-users matched by age, sex and general practitioner in Tayside, Scotland, were followed up for mortality during a period of four years (Beardon *et al.*, 1988). Mortality due to neoplasms of the digestive organs and peritoneum was markedly increased in the cimetidine takers, with a RR of 2.7 (95% confidence interval, 1.6-4.7) based on 49 deaths. The largest excesses were seen for neoplasms of the oesophagus, stomach and pancreas. Mortality from all causes among cimetidine users was increased only during the first two years of follow-up [corresponding data by duration of follow-up were not presented for cancer]. There was no significant increase in mortality due to neoplasms of respiratory and intrathoracic organs (32 deaths; RR, 1.1; 95% confidence interval, 0.67-1.8) or other neoplasms.

[The Working Group noted, as did the authors of the relevant studies, that in the case reports and studies undiagnosed gastric and intra-abdominal neoplasms could have been responsible for the symptoms that led to use of cimetidine. This possibility is supported by the short interval between exposure and observation of increased RRs and by the decreasing risks for intra-abdominal cancer, particularly gastric cancer, with time. The maximal interval that follow-up studies have so far covered is only eight years.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Cimetidine is a histamine H_2-receptor antagonist which inhibits gastric acid secretion. Since its introduction in the mid-1970s, it has been used widely by oral administration for the treatment of duodenal and gastric ulcers.

Although cimetidine can be nitrosated *in vitro* in the presence of nitrite under acidic conditions to form *N*-nitrosocimetidine, no study in experimental animals or in humans has demonstrated that this reaction occurs *in vivo*.

4.2 Experimental carcinogenicity data

Cimetidine was tested for carcinogenicity by oral administration in single studies in mice, rats and dogs. In the experiment in mice, dams were treated throughout life beginning two weeks prior to pregnancy, with no increase in tumour incidence. In female progeny that were exposed throughout life from conception, there was an increase in the incidence of lymphomas, although these tumours also occurred at relatively high rates in control animals. In rats, an increase in the incidence of benign Leydig-cell tumours of the testis was observed in the low- and high-dose groups but not in the mid-dose group. The study in dogs was inadequate for evaluation.

In a study in which mice were exposed from conception throughout life to a combination of cimetidine and sodium nitrite, males had an increased incidence of lung neoplasms, although these tumours also occurred at a high frequency in control animals.

N-Nitrosocimetidine was tested for carcinogenicity by oral administration in mice and rats and by skin application in mice. The experiments in rats and three of the studies in mice were inadequate for evaluation. In one study by oral administration in mice, there was no increase in the incidence of tumours.

4.3 Human carcinogenicity data

In a large number of case reports, cancer, particularly gastric cancer, was diagnosed at various intervals after the start of cimetidine therapy. These reports are difficult to interpret because gastric cancer is a common malignancy and cimetidine is a commonly used drug, and coincidence cannot be ruled out.

Three cohort studies showed increased incidences of gastric cancer but also of other gastrointestinal cancers among cimetidine users; however, as for the case reports, the association could well have been due to the drug being given for symptoms of pre-existing cancers. This interpretation is supported by a diminution

of the association with increasing duration of follow-up. Two of the studies also showed an association between cimetidine use and lung cancer, but confounding with cigarette smoking could well have been the explanation.

4.4 Other relevant data

Cimetidine has been associated with reversible impotence and other anti-androgenic effects in men.

N-Nitrosocimetidine is rapidly converted to cimetidine *in vivo* in experimental animals.

Cimetidine did not induce single-strand breaks in DNA from rats treated *in vivo*, nor did it methylate DNA in a variety of tissues of rats *in vivo*. It did not induce single-strand breaks in the DNA of rat cells treated *in vitro*. Cimetidine was not mutagenic to and did not cause DNA damage in *Salmonella typhimurium* or *Escherichia coli*. Cimetidine hydrochloride induced single-strand breaks and unscheduled DNA synthesis in rat but not human cells *in vitro*. It did not cause sister chromatid exchange in human cells *in vitro*.

Cimetidine in combination with sodium nitrite did not induce DNA damage *in vivo* or methylate DNA in a variety of tissues of rats *in vivo*. Gastric juice from cimetidine-treated patients was mutagenic to bacteria when enriched with nitrite.

N-Nitrosocimetidine has not been demonstrated in gastric juice of humans; however, increased gastric concentrations of nitrite and total *N*-nitroso compounds have been reported in some studies of patients taking cimetidine. *N*-Nitroso-cimetidine induced DNA damage, sister chromatid exchange, chromosomal aberrations and morphological transformation in mammalian cells *in vitro* and caused DNA damage and mutation in bacteria. Radiolabelled *N*-nitrosocimetidine methylated DNA in a variety of tissues of rats *in vivo*. (See Appendix 1.)

4.5 Evaluation[1]

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

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

Overall evaluation

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

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[1]For description of the italicized terms, see Preamble, pp. 26–29.

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