FUROSEMIDE (FRUSEMIDE)

1. Chemical and Physical Data

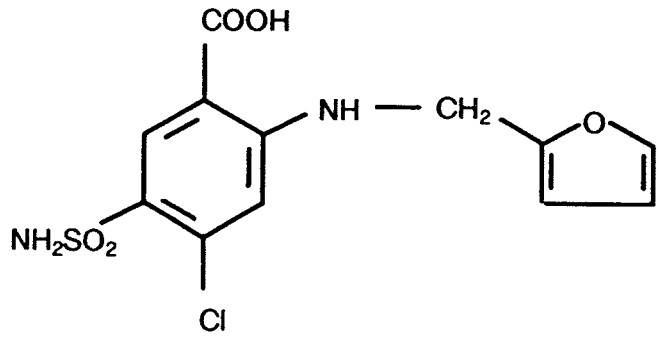
1.1 Synonyms

Chem. Abstr. Services Reg. No.: 54-31-9

Chem. Abstr. Name: 5-(Aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)-amino]-benzoic acid

Synonym: Sulfamoylanthranilic acid, 4-chloro-*N*-furfuryl-5

1.2 Structural and molecular formulae and molecular weight



$C_{12}H_{11}ClN_2O_5S$ Mol. wt: 330.77

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: White, microcrystalline powder; crystals from aqueous ethanol (Reynolds, 1989)

(*b*) *Melting-point*: 206°C dec (Windholz, 1983)

(*c*) *Solubility*: Slightly soluble in water; soluble in aqueous solutions above pH 8; slightly soluble in chloroform, ethanol and diethyl ether; soluble in acetone, methanol and dimethylformamide (Windholz, 1983)

(*d*) *Spectroscopy data*: Ultraviolet and infrared spectra have been reported (Anon., 1979).

(*e*) *Stability*: Discolours on exposure to light (Barnhart, 1989); precipitates with calcium gluconate, ascorbic acid, tetracyclines, urea and adrenaline (Windholz, 1983)

(*f*) *Dissociation constant*: $pK_a = 3.9$ (Anon., 1979)

1.4 Technical products and impurities

Trade names: Aluzine; Aquamide; Aquasin; Arasemide; Discoid; Diural; Diuresal; Diurolasa; Dryptal; Durafurid; Errolon; Franyl; Frusetic; Furetic; Furix; Furo-basan; Fur-O-Ims; Furo-Puren; Furose; Furoside; Fusid; Hydrex; Hydro-rapid; Impugan; Lasiletten; Lasilix; Lasix; Laxur; Min-I-Jet Frusemide; Moilarorin; Neo-Renal; Nicorol; Novosemide; Odemase; Oedemex; Promedes; Puresis; Seguril; Sigasalur; SK-Furosemide; Uremide; Urex; Urex-M; Uritol

The following names have been used for multi-ingredient preparations containing furosemide: Diumide-K; Frumil; Frusene; Lasikal; Lasilactone; Lasipressin; Lasix + K; Lasoride

Furosemide is available as tablets (20 mg, 40 mg, 80 mg) with lactose, magnesium stearate, starch and talc (see IARC, 1987), and for injection in 2-, 4- and 10-ml ampoules containing furosemide at 10 mg/ml sterile solution in amber vials (water and sodium hydroxide). It is also available as an oral solution containing furosemide at 10 mg/ml and 11.5% alcohol, D & C Yellow #10, FD & C Yellow #6, glycerine, parabens, sodium hydroxide and sorbitol (Barnhart, 1989).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Furosemide is prepared from 4,6-dichlorobenzoic acid-3-sulfonylchloride *via* a multistep synthesis involving the sequential addition of ammonia and 6-furfurylamine (Sturm *et al.*, 1962). It is synthesized in Brazil, Bulgaria, China, Hungary, Israel, Italy, Poland, Switzerland and the USA (Chemical Information Services, 1989-90).

Specific data on production of furosemide are not available, but the number of prescriptions for this drug in the USA increased from 16 million in 1973 to 23 million in 1981. The oral form (Lasix) alone was the eighth most frequently prescribed drug in the USA in 1985 (La Piana Simonsen, 1989). In Sweden, furosemide was sold at a level of 44.08 defined daily doses per 1000 inhabitants in 1988 (Apoteksbolaget, 1988, 1989). In Finland, furosemide sales were 13.87 defined daily doses (40 mg) per 1000 inhabitants in 1987 (Finnish Committee on Drug Information and Statistics, 1987).

Furosemide is not known to occur naturally.

2.2 Use

Furosemide is a potent, short-acting diuretic (Weiner & Mudge, 1985). It is used for the treatment of oedema of cardiac, hepatic or renal origin and in a variety of situations ranging from the control of hypertension to the symptomatic treatment of hypercalcaemia.

Furosemide has a steep dose-effect curve, and therapeutic doses range from 40 to 200 mg daily in adults (Weiner & Mudge, 1985). Treatment of oedema is usually started with an initial oral dose of 40 mg daily; in severe cases, a gradual increase up to 600 mg daily may be required. Intramuscular or slow intravenous injections of furosemide are also used, although the oral route is preferred. In the management of oliguria in acute or chronic renal failure, doses up to 6 g have been given in slow (less than 4 mg per min) intravenous infusions (see Reynolds, 1989).

The usual dose for children is 1-3 mg/kg bw daily given orally and 0.5-1.5 mg/kg bw by injection (Reynolds, 1989).

2.3 Analysis

Furosemide has been determined in biological fluids by high-performance liquid chromatography with detection by spectrofluorimetry (Uchino *et al.*, 1984; Sood *et al.*, 1987) and ultraviolet (Andreasen *et al.*, 1981) and mass spectrometry (Uchino *et al.*, 1984). Analysis of furosemide in pharmaceutical preparations by high-performance liquid chromatography and colorimetric complexation with copper has been reported (Mishra *et al.*, 1989; US Pharmacopeial Convention, Inc., 1989).

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

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 50 male and 50 female B6C3F1 mice, eight weeks old, were fed furosemide (99% pure, USP grade) at 0, 700 or 1400 mg/kg of diet for 104 weeks. The average amounts of furosemide consumed per day were approximately 100 and 200 mg/kg bw for low- and high-dose groups, respectively. Mean body weights of treated and control mice were comparable. Final survival rates in males were:

control, 31/50; low-dose, 24/50; and high-dose, 26/50; and those in females were: control, 36/50; low-dose, 29/50; and high-dose, 18/50. Survival in high-dose females was significantly lower than that in controls ($p = 0.003$). All survivors were killed at weeks 105-107 then necropsied, and about 40 different tissues were examined microscopically. In female mice, a small but statistically significant increase in the incidence of mammary gland carcinomas was observed: control, 0/50; low-dose, 2/50; and high-dose, 5/48 ($p = 0.01$, logistic regression test for trend taking account of survival) (National Toxicology Program, 1989).

Rat: Groups of 50 male and 50 female F344/N rats, seven weeks old, were fed furosemide (99% pure; USP grade) at 0, 350 or 700 mg/kg of diet for 104 weeks. The average amounts of furosemide consumed per day were approximately 15 and 30 mg/kg bw for low- and high-dose groups, respectively. Mean body weights of treated and control mice were comparable. Survivors at 104-106 weeks in males were: controls, 17/50; low-dose, 17/50; and high-dose, 20/50; those in females were: controls, 35/50; low-dose, 31/50; and high-dose, 34/50. About 40 different tissues were examined microscopically. No statistically significant increase in the incidence of tumours at any site was reported; however, in males, meningiomas of the brain were observed in 3/50 low-dose rats *versus* 2/1928 in historical controls. The authors noted that these rare tumours occurred early in the study in low-dose animals (National Toxicology Program, 1989).

(*b*) *Administration with known carcinogens*

Rat: Four groups of 25 male Fischer 344 rats, five weeks of age, were given drinking water containing 0.01% or 0.05% *N*-nitrosobutyl-*N*-(4-hydroxybutyl)-amine (NBHBA) for four weeks, followed by no further treatment or administration of furosemide [purity unspecified] dissolved in 0.5% carboxymethyl cellulose by gavage three times per week for 32 weeks (total dose, 250 mg/kg bw). The experiment was terminated at 36 weeks. One group of 25 male rats was treated with furosemide alone. No treatment-related mortality was observed in any group, but body weights of furosemide-treated groups were significantly lower; almost all rats survived to the end of the experiment. Following sacrifice, all bladders were examined histologically. No significant difference in the incidence of bladder lesions (simple, papillary or nodular hyperplasia, papillomas or carcinomas) was seen in furosemide-treated *versus* other groups. Treatment with furosemide alone did not induce any lesion in the bladder (Shibata *et al.*, 1989). [The Working Group noted the short duration of the study and the limited pathological examination.]

3.2 Other relevant data

(*a*) *Experimental systems*

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

After oral administration of furosemide to dogs, about 50% of the dose was absorbed (Yakatan *et al.*, 1979). In one study in male Sprague-Dawley rats, the bioavailability of oral furosemide was estimated to be 30% (Lee & Chiou, 1983).

The pharmacokinetics of the disappearance of furosemide from the blood is best described by two- or three-compartment open models, with dose-dependent variations in plasma protein binding (Hammarlund & Paalzow, 1982). In rats, furosemide is cleared from the plasma by the kidneys, is biotransformed by the liver or is excreted unchanged in the bile, with subsequent intestinal reabsorption (Kitani *et al.*, 1988). About 4% of furosemide administered intravenously to rats was recovered from the gut (Lee & Chiou, 1983). In contrast, biliary excretion of furosemide has been reported to be as high as 30% of doses of 50-100 mg/kg bw given to male Swiss mice (Spitznagle *et al.*, 1977). Glucuronidation of furosemide appears to take place in the kidney; removal of the liver did not affect clearance of furosemide in dogs (Lee & Chiou, 1983; Verbeeck *et al.*, 1981).

Covalent binding of furosemide to mouse liver proteins has been shown, and this was enhanced by administration of an inhibitor of epoxide hydrase, suggesting formation of an arene oxide intermediate involving the furan ring (Wirth *et al.*, 1976). *In vitro*, human liver microsomes can convert furosemide to metabolites that bind irreversibly to microsomal proteins (Dybing, 1977).

Formation of unidentified metabolites was demonstrated after incubation of furosemide with a 9000 × *g* supernatant fraction of washed stomach homogenates from rats. The apparent metabolism per gram of tissue was greater in the stomach than in the small intestine, large intestine or liver (Lee & Chiou, 1983).

(ii) *Toxic effects*

The oral LD_{50} for furosemide was approximately 2700 mg/kg bw in 60-day-old rats (Goldenthal, 1971), 2200 mg/kg bw in mice (Romanova & Rudzit, 1985) and 800 mg/kg bw in rabbits (Horioka *et al.*, 1982). The intravenous LD_{50} in rabbits was 800 mg/kg (Horioka *et al.*, 1982). Intraperitoneal injection of 400 mg/kg bw into male mice produced massive necrosis in both the midzonal and centrilobular areas of the liver; this damage was prevented by prior administration of cytochrome P450 inhibitors (Mitchell *et al.*, 1974).

Two of five male and three of five female rats that were fed diets containing furosemide at up to 46 g/kg for 14 days died before the end of the studies. Minimal-to-mild nephrosis was found in all rats that received furosemide at 1.3 or 46 g/kg and in one male receiving 5.1 g/kg. Microscopically, the toxic lesion was subcapsular or cortical and was characterized by tubular-cell regeneration;

mineralization was present at the corticomedullary junction. Dose-related nephrosis was also observed in mice in a 14-day study. In a 13-week study, male rats given a diet containing furosemide at 12.5 g/kg or more and females given a diet containing 15 g/kg had increased liver:body weight ratios; dose-related diuresis was also observed. Compound-related minimal-to-moderate nephrosis occurred in male rats given 5 or 10 g/kg and in females given 7.5 or 15 g/kg. Mineralization was observed at the corticomedullary junction in male rats given 0.625 g/kg or more. In mice, dose-related minimal-to-mild nephrosis was also observed in a 13-week study (National Toxicology Program, 1989).

In a two-year study (see section 3.1), nephropathy occurred with greater severity in dosed male rats than in non-dosed rats. In mice, compound-related nephropathy and dilatation of the renal pelvis occurred in males and females; and tubular cysts, suppurative inflammation and epithelial hyperplasia of the renal pelvis were observed. Epithelial hyperplasia and inflammation of the urinary bladder and suppurative inflammation of the prostate were seen in dosed male mice; and suppurative inflammation of the ovary, uterus and adrenal cortex was observed at increased incidence in high-dose female mice (National Toxicology Program, 1989).

Subcutaneous doses of furosemide at 5 or 15 mg/kg bw per day were given to Sprague-Dawley pups from day 4 to day 28 after birth. Increased urinary calcium and magnesium excretion was observed, and the total concentration of calcium and magnesium in bone was lower. The growth of the pups was inhibited in a dose-dependent manner, and bone mineral content was appropriate for the smaller bone mass (Koo *et al.*, 1986).

Furosemide at 0.5 mM reduced the viability of isolated mouse hepatocytes and induced ultrastructural changes related to toxicity (Massey *et al.*, 1987).

Haemodynamic effects include an increase in renal blood flow (Hook *et al.*, 1965) and decreases in mesenteric (Gaffney *et al.*, 1978), hepatic (Gaffney *et al.*, 1979) and splenic (Gaffney & Williamson, 1979) blood flow.

(iii) *Effects on reproduction and prenatal toxicity*

When CRCD rats were administered furosemide at 37.5, 75, 150 or 300 mg/kg bw twice daily on days 6-17 of gestation [route of administration unspecified], the two highest dose levels, which caused maternal deaths, resulted in increased resorption rates and decreased fetal weights. Dose-related increases in the frequency of wavy ribs occurred in all treatment groups. In addition, five of 176 fetuses in the group receiving 150 mg/kg bw had malformations of the scapula (Robertson *et al.*, 1981).

(iv) *Genetic and related effects*

Furosemide was not mutagenic to *Salmonella typhimurium* in plate incorporation tests in the presence or absence of an exogenous metabolic system (National Toxicology Program, 1989).

The urine of rats treated *in vivo* with furosemide at 45 mg/kg bw did not induce gene conversion in growing cells of *Saccharomyces cerevisiae* D4-RDII (Marquardt & Siebert, 1971).

Furosemide was reported to induce mutations to trifluorothymidine resistance in L5178Y mouse lymphoma cells in the presence of an exogenous metabolic system only at the highest concentration tested (1500 μg/ml). It was also reported to induce sister chromatid exchange and chromosomal aberrations in Chinese hamster CHO cells at 3750 and 5000 μg/ml in the presence and absence of an exogenous metabolic system (National Toxicology Program, 1989). [The Working Group noted the exceptionally high concentrations used in these studies, surpassing the solubility limits of the test substance, which preclude an assessment of the observed effects.] No sister chromatid exchange was induced in a diploid human fibroblast cell line (HE2144) by concentrations of up to 0.33 mg/ml (Sasaki *et al.*, 1980). Furosemide induced chromosomal damage in Chinese hamster lung fibroblasts *in vitro*, but only in the absence of an exogenous metabolic system (Matsuoka *et al.*, 1979; Ishidate, 1988). A concentration-dependent increase in the frequency of chromosomal aberrations was observed in human lymphocytes exposed *in vitro* to furosemide for 24 and 72 h (Jameela *et al.*, 1979). No such effect was detected in the human fibroblast cell line HE2144 (Sasaki *et al.*, 1980).

In male C3H/HE mice treated intraperitoneally with furosemide at 0.3-50 mg/kg bw, a non-dose-dependent increase in the percentage of meiotic cells with chromosomal aberrations was observed during the whole spermatogenic cycle, i.e., in weeks 1-5 after treatment (Subramanyam & Jameela, 1977). [The Working Group noted that only one mouse per dose per week was apparently used.]

(*b*) *Humans*

(i) *Pharmacokinetics*

In healthy subjects, the bioavailability of furosemide ranges from 60 to 69% (Kelly *et al.*, 1973; Rupp, 1974; Tilstone & Fine, 1978); but in end-stage renal failure its availability is reduced to 43-46% (Rane *et al.*, 1978; Tilstone & Fine, 1978). According to early reports, food does not alter bioavailability, although the rate of absorption is decreased (Kelly *et al.*, 1973). In a recent study, however, a reduction of approximately 30% in bioavailability, accompanied by a reduced diuretic effect, was observed when furosemide was given at 40 mg to ten healthy volunteers with breakfast as compared to when it was given in the fasting state (Beermann & Midskov, 1986).

About 99% of furosemide is bound to plasma proteins (Smith *et al.*, 1980), almost exclusively to albumin (Andreasen & Jacobsen, 1974; Prandota & Pruitt, 1975; Branch, 1983).

Two-compartment models are most often used to describe the kinetics of furosemide (Rupp, 1974; Beermann *et al.*, 1975). The half-time of the α-phase averages 10-15 min and that of the β-phase, 47-90 min (Beermann *et al.*, 1977; Mikkelsen & Andreasen, 1977; Rane *et al.*, 1978; Andreasen *et al.*, 1982). The apparent volume of distribution at steady state is approximately 190 ml/kg (Mikkelsen & Andreasen, 1977; Andreasen *et al.*, 1978). The plasma clearance of furosemide is 2.2-3.0 ml/min per kg (Mikkelsen & Andreasen, 1977; Andreasen *et al.*, 1978). A higher non-renal clearance ratio is seen after oral dosing (15.7 ± 4.8%) than after intravenous administration (11.2 ± 4.0%) (Zhu & Koizumi, 1987). Glucuronide conjugate is the only well documented metabolite of furosemide in man (Beermann *et al.*, 1975; Andreasen & Mikkelsen, 1977; Verbeeck *et al.*, 1982).

About 20% of furosemide is eliminated by renal glucuronidation (Smith *et al.*, 1980); it has been suggested that the remaining 25-30% may be secreted into the gut in unchanged and/or conjugated form (Branch, 1983). However, gastrointestinal elimination amounted to only 2% of renal clearance, and active secretion into the intestinal lumen did not occur in six healthy volunteers given furosemide as a 40-mg bolus followed by a continuous infusion of 0.55 mg/kg per h. Plasma clearance was 223 ± 15, renal clearance, 93.1 ± 21.2 and total clearance by the gastrointestinal tract, 2.1 ± 0.2 ml/min. There was no change in the intestinal clearance of furosemide after administration of probenecid, but plasma and renal clearance decreased by 48 and 70%, respectively. It was also shown that incubation of urine samples with β-glucuronidase increased furosemide levels (Valentine *et al.*, 1986).

The disposition of furosemide during renal insufficiency, nephrotic syndrome, cirrhosis and congestive heart failure has been reviewed (Brater, 1986). The mean plasma half-time of furosemide in patients with nephrosis does not differ from that in normal subjects but is prolonged about three fold in patients with uraemia (Rane *et al.*, 1978). A positive relationship between the renal clearance of creatinine and of furosemide has been shown (Beermann *et al.*, 1977). Liver disease may prolong plasma half-time by up to 4.3 h, depending on the degree of liver failure (Allgulander *et al.*, 1980; Fuller et al., 1981; Verbeeck *et al.*, 1982).

(ii) *Adverse effects*

The most common adverse effects of furosemide are fluid and electrolyte imbalance, including hyponatraemia, hypokalaemia and hypochloraemic alkalosis. Hyperuricaemia is relatively common, and a variety of uncommon adverse reactions have been reported (see Reynolds, 1989).

Signs of volume depletion and hypokalaemia have been reported in several studies (Greenblatt *et al.*, 1977; Naranjo *et al.*, 1978; Spino *et al.*, 1978; Lowe *et al.*, 1979). Rare adverse effects reported in patients receiving furosemide include skin rash, thrombocytopenia (Lowe *et al.*, 1979), gynaecomastia (Tuzel, 1981), temporary hearing impairment (Naranjo *et al.*, 1978; Spino *et al.*, 1978) and hepatic coma in cirrhotic patients (Naranjo *et al.*, 1978). Elevated serum concentrations of parathyroid hormone and alkaline phosphatase, together with decreased calcium concentration, were shown in 36 patients with congestive heart failure (Elmgreen *et al.*, 1980).

Renal calcification was documented in ten premature infants who had received furosemide in a dose of at least 2 mg/kg bw per day for at least 12 days (Hufnagle *et al.*, 1982).

(iii) *Effects on reproduction and prenatal toxicity*

No report of pregnancy outcomes following first-trimester use of furosemide has been found. Furosemide has been used extensively for treatment of oedema, hypertension and heart failure in the later stages of pregnancy, with no apparent adverse effect on the fetus or newborn (see review by Briggs *et al.*, 1986).

(iv) *Genetic and related effects*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

In a hypothesis-generating cohort study designed to screen a large number of drugs for possible carcinogenicity [described in detail in the monograph on ampicillin], 2302 persons to whom at least one prescription for furosemide had been dispensed during 1969-73 were followed up for up to 15 years (Selby *et al.*, 1989). Increased risks were noted for cancer of the lung (50 observed, 25.4 expected; $p < 0.002$) and for cancers at all sites combined (233 observed, 164.5 expected; $p < 0.002$). [The Working Group noted that heart failure and cirrhosis of the liver, both of which are associated directly or indirectly with cigarette smoking, are frequent indications for prescribing furosemide, and confounding by cigarette smoking (which was not analysed in the study) may explain the observed associations.] In an earlier report with up to nine years of follow-up (Friedman & Ury, 1983), there was also an association with cancer of the liver (5 observed, 1.6 expected cases; $p < 0.05$). The medical records indicated that this association was due to underlying liver disease for which furosemide was prescribed. [The Working Group noted, as did the authors, that, since some 12 000 comparisons were made in this study, the associations should be verified independently. Data on duration of use were not provided.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Furosemide is a diuretic. It has been used extensively since 1964 in the treatment of oedema and hypertension.

4.2 Experimental carcinogenicity data

Furosemide was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats. A small increase in the incidence of mammary gland carcinomas was observed in female mice. No increase in the incidence of tumours was seen in rats.

4.3 Human carcinogenicity data

In one hypothesis-generating study in which many drugs were screened for possible carcinogenicity, associations with furosemide use were observed for cancers of the lung and of all sites combined, which could have been accounted for by smoking and/or chance.

4.4 Other relevant data

The data are inadequate to assess the effects of furosemide on human reproduction. In rats, the drug induces skeletal anomalies.

Furosemide is metabolized by mouse and human liver microsomes and binds covalently to proteins. Renal tubular hyperplasia and hepatic centrilobular necrosis have been observed after administration of large doses of furosemide to mice.

Studies on the induction by furosemide of chromosomal aberrations in mice were inconclusive. Reports of studies on chromosomal aberrations in human cells *in vitro* gave conflicting results; it induced chromosomal damage in hamster cells. Furosemide did not induce sister chromatid exchange in human cells *in vitro*; one study gave questionably positive results for sister chromatid exchange in Chinese hamster cells and for gene mutation in mouse lymphoma cells. The urine of rats treated with this drug did not induce gene conversion in *Saccharomyces cerevisiae*. It was not mutagenic to *Salmonella typhimurium*. (See Appendix 1.)

4.5 Evaluation[1]

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

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

Overall evaluation

Furosemide *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. 26–29.

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