NITROFURANTOIN

1. Chemical and Physical Data

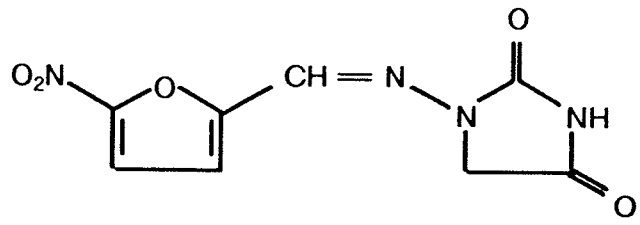
1.1 Synonyms

Chem. Abstr. Services Reg. No.: 67-20-9; 17140-81-7 (monohydrate); 54-87-5 (sodium salt)

Chem. Abstr. Name: 2,4-Imidazolidinedione, 1-{[(5-nitro-2-furanyl)methylene]amino}-

Synonyms: 1-[(5-Nitrofurfurylidene)amino]imidazolidine-2,4-dione; 1-[(5-nitrofurfurylidene)amino]hydantoin

1.2 Structural and molecular formulae and molecular weight



$C_8H_6N_4O_5$ Mol. wt: 238.16

1.3 Chemical and physical properties of the pure substance

From Cadwallader and Jun (1976) and Windholz (1983)

(*a*) *Description*: Pale orange-yellow needles from dilute acetic acid

(*b*) *Melting-point*: 270-272°C (decomposes)

(*c*) *Solubility*: Solubilities of nitrofurantoin in many aqueous media and organic solvents have been reported.

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

(*e*) *Stability*: Tablets and suspension stable for five years at room temperature in regular glass containers; crystals and solutions discoloured by alkali and by exposure to light

(*f*) *Dissociation constant*: $pK_a = 7.2$

1.4 Technical products and impurities

Trade names: Berkfurin; Chemiofuran; Chemiofurin; Cistofuran; Cyantin; Cystit; Dantafur; Fua-Med; Furadantin; Furadantina; Furadantine; Furadöine; Furadonine; Furandoninium; Furalan; Furantoin; Furantoina; Furatin; Furedan; Furil; Furobactina; Furophen; Gurachel; Ituran; Ivadantin; Microdoin; Micturol Simple; Nephronex; Nierofu; Nifuran; Nitrex; Nitrofor-50; Nitrofor-100; Nitrofurantonum; Nitrofurin; Novofuran; N-Toin; Orafuran; Parfuran; Phenurin; Sarodant; Trantoin; Trocurine; Urantoin; Urefuran; Uretoin; Uriston; Urizept; Urodil; Urodin; Urolisa; Urolong; Urosagen; UroTablinen; Uro-Tablinen; Urotoin; Uvamine; Welfurin; Zoofurin

Macrocrystalline products: Furadantin MC; Macrodantin; Uvamin retard

Nitrofurantoin is available as tablets (50 mg and 100 mg) and as a suspension (Barnhart, 1989; Reynolds, 1989). Impurities in the tablets include calcium pyrophosphate, magnesium stearate, starch and sucrose; and those in the suspension include carboxymethyl cellulose, sodium citric acid, glycerine, magnesium aluminium silicate, methylparaben, propylparaben, saccharin (see IARC, 1987a), sodium citrate and sorbitol. Nitrofurantoin is available from at least one manufacturer in macrocrystalline form (Cunha, 1988).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Nitrofurantoin can be prepared from 1-aminohydantoin sulfate or hydrochloride and 5-nitro-2-furaldehyde diacetate in isopropyl alcohol (see IARC, 1987b) media (Cadwallader & Jun, 1976). It is synthesized in China, India, Italy, the Netherlands and Spain (Chemical Information Services, 1989-90). In Sweden, sales of nitrofurantoin in 1988 were 0.09 defined daily doses per 1000 inhabitants (Apoteksbolaget, 1988, 1989).

Nitrofurantoin is not known to occur naturally.

2.2 Use

Nitrofurantoin is used extensively in the treatment and prophylaxis of uncomplicated lower urinary-tract infections. The usual oral dose for adults is 50-100 mg four times daily, with meals and at bedtime. Treatment is usually continued for 14 days. The daily dose for children is 5-7 mg/kg given in four divided

oral doses. The dosage is reduced if continued beyond 14 days or if used for prophylaxis (Reynolds, 1989). In long-term treatment, a dose as low as 1 mg/kg may be used (Lohr *et al.*, 1977). A single dose of 50-100 mg at bedtime may be sufficient to prevent recurrences (Stamey *et al.*, 1977).

2.3 Analysis

Analytical methods have been described for nitrofurantoin in pharmaceutical formulations using thin-layer chromatography (Cadwallader & Jun, 1976), high-performance liquid chromatography (US Pharmacopeial Convention, Inc., 1989), polarography (Surmann & Aswakun, 1985; Morales *et al.*, 1987) and electrochemical methods (Fogg & Ghawji, 1988). Methods for analysing the compound in plasma and urine include high-performance liquid chromatography (Vree *et al.*, 1979), polarography (Morales *et al.*, 1987) and electrochemical analysis (Mason & Sandmann, 1976).

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

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 52-53 male and 54 female (C57Bl/6N × DBA/2N)F_1(BDF_1) mice, nine weeks of age, were administered nitrofurantoin [purity and crystalline form unspecified] at 0, 750 or 3000 mg/kg of diet for 104 weeks, when the experiment was terminated. At that time, survival in males and females combined was 50.5%, 42.5% and 46.2% in control, low-dose and high-dose groups, respectively. Administration of the high dose significantly lowered body weights in mice of each sex in comparison with controls. In males, a reduced incidence of hepatic adenomas was observed: 6/53 controls, 1/52 low-dose and 0/52 high-dose mice (p = 0.014, Fisher's exact test). No increase in the incidence of tumours at any site was observed (Ito *et al.*, 1983).

Groups of 50 male and 50 female Swiss (Crl:CD^R-1(ICR)BR) mice, about 50 days of age, received nitrofurantoin (pharmaceutical grade macrocrystals) at 0, 50, 100 or 200 mg/kg of diet for 22 months. Increased mortality was observed in males treated with the high-dose. In males, the incidences of malignant lymphomas at all sites were: controls, 2/50; low-dose, 6/50; mid-dose, 4/49; and high-dose, 10/50 [p = 0.014, Fisher's exact test; p = 0.012, Cochran-Armitage trend test] (Butler *et al.*, 1990).

Groups of 50 male and 50 female B6C3F$_1$ mice, eight to nine weeks of age, were fed nitrofurantoin (pharmaceutical grade) at 0, 1300 or 2500 mg/kg of diet for 103 weeks. Survival at termination of the experiment was reduced in control females: controls, 19/50; low-dose, 37/50; and high-dose, 37/50. Mean body weights of male and female high-dose mice were 12% lower than those of controls. In females, ovarian atrophy was seen in 0/50 control, 48/50 low-dose and 49/50 high-dose animals. Controls had ovarian abscesses (18/50) and suppurative inflammation of the uterus (11/50). There was no significant increase in the incidence of any individual type of tumour; however, when tubular adenomas and benign mixed tumours of the ovary are combined, the incidence is significant: 0/50 controls, 0/50 low-dose and 9/50 high-dose ($p = 0.01$, incidental tumour test) (National Toxicology Program, 1989). [The Working Group noted the poor survival and the high incidence of ovarian abscesses in the controls.]

In a study of ovarian atrophy, three groups of female B6C3F$_1$ mice, five to six weeks of age, were given nitrofurantoin (pharmaceutical grade) at 0, 350 or 500 mg/kg bw daily in the diet for 64 weeks. Intermittent sacrifices were made at 4, 8, 13, 17 and 47 weeks; the numbers of mice still alive at 65 weeks were 20 controls, 19 low-dose and 18 high-dose animals. Treated animals gained significantly less weight than the controls. There was no increase in the incidence of neoplasms of the reproductive system [the only tissues reported]. By week 43, there was evidence of ovarian atrophy in treated females; by the end of the study, the incidences were: control, 0/20; low-dose, 18/19; and high-dose, 18/18 (Stitzel *et al.*, 1989). [The Working Group noted the short duration of the study and the small number of animals used.]

Rat: A group of weanling female Sprague-Dawley rats (36 animals alive at ten weeks), weighing 40-72 g, was administered nitrofurantoin ('pure'; identity and purity checked by infrared and ultraviolet absorption spectrophotometry, melting-point and paper chromatography) at 1870 mg/kg of diet for 16 weeks, after which time the dose was reduced to 1000 mg/kg of diet in weeks 16-75 due to impaired growth and premature mortality. The experiment was terminated at week 80. A group of untreated rats served as controls (30 alive at ten weeks). No increase in tumour incidence was observed (Cohen *et al.*, 1973). [The Working Group noted the short duration of the experiment and the small number of effective animals.]

Two groups of 11-12 weanling, germ-free female Sprague-Dawley rats, weighing 85-100 g, were fed nitrofurantoin (extracted from pharmaceutical grade, macrocrystalline nitrofurantoin) at 0 or 1880 mg/kg of diet for 104 weeks. The growth rate in treated rats was slightly retarded as compared with that in controls. The median survival time was 96 weeks for controls and 90 weeks for treated animals. The incidences of mammary fibroadenomas were 2/11 controls and 9/12 treated rats ($p < 0.01$, Fisher's exact test). No increase in the incidence of tumours

at other sites was observed (Wang *et al.*, 1984). [The Working Group noted the small number of animals used.]

Groups of 50 male and 50 female Fischer 344 rats, six to seven weeks of age, were given nitrofurantoin (pharmaceutical grade) at 0, 600 or 1300 mg/kg bw (females) and 0, 1300 or 2500 mg/kg (males) of diet for 103 weeks. Mean body weights were similar in control and treated animals. Survival at termination of the experiment was: males—control, 24/50; low-dose, 27/50; and high-dose, 26/50; females—control, 25/50; low-dose, 26/50; and high-dose, 31/50. Chronic tubular nephropathy was observed in all treated rats. In males, the incidence of mainly microscopic renal tubular adenomas was 3/50 controls, 11/50 low-dose [$p = 0.02$, Fisher's exact test] and 19/50 [$p < 0.001$; Fisher's exact test] high-dose animals [$p < 0.001$, Cochran-Armitage test for trend]. Renal tubular carcinomas were seen in two high-dose males. Osteosarcomas were seen in one low-dose and two high-dose males. Reductions in the incidences of a number of neoplasias were observed in males: preputial gland adenomas—control, 6/48; low-dose, 5/50; and high-dose, 0/47 ($p = 0.018$, incidental tumour test); preputial gland carcinomas—control, 6/48; low-dose, 6/50; and high-dose, 0/47 ($p = 0.028$, incidental tumour test); and interstitial-cell adenomas of the testis—control, 47/50; low-dose, 45/50; and high-dose, 21/50 ($p < 0.001$, incidental tumour test). No change in tumour incidence was observed in females (National Toxicology Program, 1989). [The Working Group was not convinced of the neoplastic nature of the microscopic kidney lesions.]

(*b*) *Transplacental administration*

Mouse: A group of 10 pregnant ICR/Jcl mice, 10-12 weeks of age, received three subcutaneous injections of nitrofurantoin [purity unspecified] at 75 μg/g bw suspended in a 1% gelatin solution on days 13, 15 and 17 of gestation. Groups of 22 gelatin-treated and 76 untreated dams served as controls. Offspring were foster-nursed by untreated dams and were sacrificed 32 weeks after birth. Survival was comparable in treated and untreated mice at 32 weeks. The incidence of papillary adenomas of the lung in the offspring of nitrofurantoin-treated dams was 10/78, that in gelatine controls, 5/203, and that in untreated controls, 29/478 (Nomura *et al.*, 1984). [The Working Group noted that the distribution of tumours among litters was not given, that the sex of the offspring was not given and that the experiment was short.]

3.2 Other relevant data

(*a*) *Experimental systems*

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

The pharmacokinetics of nitrofurantoin have been reviewed (Conklin, 1978).

After oral or parenteral administration, nitrofurantoin is rapidly absorbed and is excreted primarily unchanged in the urine and bile of rats (Paul *et al.*, 1960; Buzard *et al.*, 1961; Veronese *et al.*, 1974; Wierzba *et al.*, 1982) and mice (Maiti & Banerjee, 1978). After intravenous administration of nitrofurantoin to dogs at 1.5-24 mg/kg bw, up to 23% was recovered from the bile, while urinary excretion accounted for up to 36% (Conklin & Wagner, 1971). In male Sprague-Dawley rats, 16-30% of a total dose of nitrofurantoin was recovered in the urine (Olivard *et al.*, 1976). After a single administration of nitrofurantoin at 25 mg/kg bw by gavage to female albino rats, 52% and 2.0% of the total dose were recovered in the urine and faeces, respectively (Paul *et al.*, 1960). Excretion of nitrofurantoin in the urine of rats has been reported to be age-dependent (Braunlich *et al.*, 1978; Wierzba *et al.*, 1982).

Intravenous administration of nitrofurantoin at 1.5-24 mg/kg bw to adult male beagle dogs weighing 10-16 kg stimulated bile excretion, and nitrofurantoin was found in bile (at 6 mg/kg bw, 22.6 ± 4.7% total dose) and urine (24.1 ± 4.7%) (Conklin & Wagner, 1971). Nitrofurantoin is excreted in bile, reabsorbed and recirculated enterohepatically (Conklin *et al.*, 1973). After intravenous administration of nitrofurantoin to rats, the plasma half-time was 25 min, and 50% was recovered in the urine as unchanged compound (Buzard *et al.*, 1961). The small intestine was considered to be the main site of absorption (Maiti & Banerjee, 1978).

4-Hydroxyfurantoin has been isolated from the urine of rats treated with nitrofurantoin (Olivard *et al.*, 1976; Streeter *et al.*, 1988). Reductive metabolism of nitrofurantoin under anaerobic conditions has been described in both rodent tissue and bacteria. In the absence of oxygen, nitrofurantoin appears to be reduced irreversibly *via* nitroso and/or hydroxylamine forms (Mason & Holtzman, 1975a; Biaglow *et al.*, 1977; Leskovac & Popovic, 1980).

Under aerobic conditions *in vitro*, reduction of nitrofurantoin stimulates consumption of oxygen and production of superoxide anion, free radicals and hydrogen peroxide in avian liver and in mammalian liver, lung, small intestine, kidney and gastrointestinal contents (Mason & Holtzman, 1975b; Biaglow *et al.*, 1977; Aufrere *et al.*, 1978; Sasame & Boyd, 1979; Leskovac & Popovic, 1980; Peterson *et al.*, 1982).

Under anaerobic conditions, microsomal and soluble fractions from rat lung and liver mediated the covalent binding of ^{14}C-nitrofurantoin-derived radioactivity to macromolecules. Covalent binding of ^{14}C-nitrofurantoin activity was greatest in the kidney, liver, ileum, lung and heart of rats (Boyd *et al.*, 1979).

(ii) *Toxic effects*

The LD_{50} of nitrofurantoin in mice was 150 mg/kg bw by intraperitoneal injection and 306 mg/kg bw by gavage (Åkerblom & Campbell, 1973).

Subcutaneous administration of nitrofurantoin to male rats caused severe pulmonary damage characterized by oedema, congestion and haemorrhage (Boyd *et al.*, 1979). Male and female rats administered nitrofurantoin orally at 20, 50 or 100 mg/kg bw twice a day were reported to develop structural and functional changes in the sciatic nerve (Behar *et al.*, 1965).

When nitrofurantoin was administered to female mice in the diet at 350 and 500 mg/kg bw and animals were examined after 4-64 weeks of treatment, a dose-related effect on body weight gain was seen as well as a reduction in uterus:brain and ovary:brain weight ratios. Histological examination revealed a dose-related decrease in the occurrence of old corpora lutea and an increase in the occurrence of intermediate and atretic follicles. The effects were more pronounced with higher dose and longer treatments. Oestrous cycles were lengthened in a dose-dependent fashion. Ovaries were atrophic and non-functioning at 43 weeks (Stitzel *et al.*, 1989).

In a 90-day toxicity study involving the administration of nitrofurantoin in the diets of rats and mice, necrosis of ovarian follicular epithelial cells was the principal pathological finding (Maronpot, 1987).

Four of five male and four of five female mice fed nitrofurantoin at 10 000 mg/kg of diet died within 14 days. No rats receiving up to 20 000 mg/kg of diet for 14 days died; treatment-related signs included inactivity, rough coats, sunken eyes, bright yellow urine and/or yellow fur. Feeding of nitrofurantoin at 10 000 mg/kg of diet to female rats for 13 weeks caused normal-to-mild necrosis of ovarian follicles; the effect was seen in a smaller proportion of animals receiving lower doses. Minimal-to-mild degeneration of the germinal epithelium of the testis was observed in male mice fed nitrofurantoin at up to 5000 mg/kg of diet for 13 weeks. Similar treatment of male mice caused minimal-to-mild necrosis of the kidney epithelium (National Toxicology Program, 1989).

In two-year studies (see section 3.1), ovarian atrophy was observed in low- and high-dose female mice, and testicular aspermatogenesis, degeneration of the germinal epithelium and atypical cells and depletion of the epididymis were observed at increased incidences in high-dose male mice. Spindle-cell hyperplasia of the adrenal cortex occurred in treated female mice, and mineralization of the renal medulla and dilatation of the renal tubules were observed in high-dose mice. Ovarian abscesses were observed in control but not in treated mice. In the two-year study in rats, fibrous osteodystrophy and mineralization of the glandular stomach occurred in treated animals. Atypical cells of the epididymis and degeneration of the testis were observed in high-dose animals; and fibrinoid necrosis of arterioles and perivascular infiltration of mononuclear cells were observed in the testis (National Toxicology Program, 1989).

(iii) *Effects on reproduction and prenatal toxicity*

Nitrofurantoin has similar toxic effects on the testis as other nitrofurans (Cohen, 1978). Rats treated with nitrofurantoin at 10 or 85 mg/kg bw by gastric intubation daily for one month showed depression of spermatogenesis, mainly at the stage of primary spermatocytes; some effect on spermatogonia was also observed. Partial regeneration had occurred by 48 days after cessation of treatment. The gonadotoxic effects could be prevented by simultaneous administration of 'cystine' (Yunda *et al.*, 1974). [The Working Group assumed that cysteine was meant.]

Testicular and ovarian degeneration was observed in F344/N rats given nitrofurantoin in the diet at a dose equivalent to 110 mg/kg bw (males) and 60 mg/kg bw (females) for 13 weeks. Testicular degeneration was observed in B6C3F1 mice given nitrofurantoin in the diet at a dose equivalent to 285 mg/kg bw for 13 weeks (National Toxicology Program, 1989).

In routine safety evaluations of nitrofurantoin macrocrystals, including studies of fertility and perinatal-postnatal effects in rats and teratogenicity in rats and rabbits, no adverse effect was observed with daily doses of 10, 20 and 30 mg/kg bw administered orally. In the fertility test, however, male rats were treated with only 10 mg/kg bw; at this dose, no adverse effect on fertility or testicular histology was observed (Prytherch *et al.*, 1984).

After subcutaneous injection of nitrofurantoin to ICR/Jcl mice at 100 or 250 mg/kg bw on days 9-11 of gestation, no increase in embryo- or fetomortality was observed, but a decrease in fetal weight occurred in the high-dose group only. A significant ($p < 0.001$) increase in the incidence of malformations (cleft palate and syndactyly) was observed in the high-dose group only (Nomura *et al.*, 1984).

(iv) *Genetic and related effects*

The mutagenicity of nitrofurans has been reviewed (Klemencic & Wang, 1978; McCalla, 1983).

Nitrofurantoin inhibited DNA synthesis in *Escherichia coli* (Lu & McCalla, 1978). It induced DNA single-strand breaks in a nitroreductase-proficient but not in a nitroreductase-deficient strain of *E. coli* (McCalla *et al.*, 1971). It induced differential toxicity in *E. coli*, *Salmonella typhimurium* and *Bacillus subtilis* in the presence and absence of an exogenous metabolic system (McCalla & Voutsinos, 1974; Yahagi *et al.*, 1974; Ebringer & Bencova, 1980; McCarroll *et al.*, 1981a,b; Suter & Jaeger, 1982; De Flora *et al.*, 1984).

Nitrofurantoin was weakly mutagenic to *E. coli* in the presence and absence of an exogenous metabolic system (McCalla & Voutsinos, 1974; Yahagi *et al.*, 1974; Setnikar *et al.*, 1976; Lu *et al.*, 1979; Ebringer & Bencova, 1980; Obaseiki-Ebor & Akerele, 1986). It was mutagenic to *S. typhimurium* TA100 and TA98, in the

presence and absence of an exogenous metabolic system (Rosenkranz & Speck, 1976; Wang & Lee, 1976; Goodman *et al.*, 1977; Chin *et al.*, 1978; De Flora, 1979; Shirai & Wang, 1980; Haworth *et al.*, 1983; De Flora *et al.*, 1984; Ni *et al.*, 1987), and to TA97 (Obaseiki-Ebor & Akerele, 1986) but not to TA1535, TA1536, TA1537 or TA1538 (Yahagi *et al.*, 1974; Haworth *et al.*, 1983; De Flora *et al.*, 1984). The strong responses in the *Salmonella* mutagenicity tests are due to the high activity of bacterial nitroreductases (Rosenkranz & Speck, 1976; Wang & Lee, 1976; Rosenkranz & Mermelstein, 1983; Ni *et al.*, 1987).

Urine of rats fed a diet containing 0.5% nitrofurantoin was mutagenic to *S. typhimurium* (Wang & Lee, 1976).

The urine of rats treated orally with nitrofurantoin at 500 or 1000 mg/kg bw induced mitotic gene conversion in *S. cerevisiae* D4-RDII (Siebert *et al.*, 1979). In a host-mediated assay with mice treated orally with nitrofurantoin at 0.3 mM/kg [72 mg/kg], no increase in the frequency of gene conversion was found in *S. cerevisiae* D4 (Setnikar *et al.*, 1976). Oral treatment of rats with nitrofurantoin at 500 mg/kg bw led to an increase in the frequency of gene conversion in *S. cerevisiae* D4-RDII (Siebert *et al.*, 1979).

Nitrofurantoin did not induce gene conversion in *Saccharomyces cerevisiae* D4 (Setnikar *et al.*, 1976). In strains D4-RDII and D7, it induced mitotic gene conversion (Siebert *et al.*, 1979; Callen, 1981). It induced non-disjunction and mitotic crossing-over in spot tests with diploid strains of *Aspergillus nidulans* (Bignami *et al.*, 1974).

Nitrofurantoin fed or injected to adult *Drosophila melanogaster* gave ambiguous results in the sex-linked recessive lethal test (Kramers, 1982; Zimmering *et al.*, 1985). It gave positive results in the wing spot test in *Drosophila*, producing large single spots (Graf *et al.*, 1989).

Nitrofurantoin inhibited DNA synthesis in mouse L-929 cells (Olive, 1979) and in diploid human fibroblasts (Hirsch-Kauffmann *et al.*, 1978). In Chinese hamster ovary (CHO K_1-BH_4 and CHO UV-5) cells, it induced mutations to 6-thioguanine resistance in the presence, but not in the absence, of an exogenous metabolic system (Gao *et al.*, 1989). Nitrofurantoin induced DNA strand breaks in mouse L cells (Olive & McCalla, 1977), in purified rat liver nuclei and in the human cell line HuF_{22} (Parodi *et al.*, 1983). It did not induce unscheduled DNA synthesis in human fibroblasts (Tonomura & Sasaki, 1973) or in rat primary hepatocytes (Williams *et al.*, 1989).

Nitrofurantoin induced sister chromatid exchange in Chinese hamster CHO cells (Shirai & Wang, 1980) but not in the human fibroblastic cell line HE 2144 (Sasaki *et al.*, 1980). It did not induce chromosomal aberrations in human lymphocytes *in vitro* (Tonomura & Sasaki, 1973) or in the human cell line HE 2144

(Sasaki *et al.*, 1980). It induced chromosomal aberrations in Chinese hamster lung (CHL) cells (Ishidate, 1988).

Intraperitoneal injection of nitrofurantoin at up to 112 mg/kg bw induced DNA strand breaks in liver (Russo *et al.*, 1982), kidney, lung and spleen cells of rats and in mouse bone-marrow cells (Parodi *et al.*, 1983). Intraperitoneal treatment at up to 64 mg/kg bw induced sister chromatid exchange in mouse bone-marrow cells *in vivo* (Parodi *et al.*, 1983).

Nitrofurantoin at 80 mg/kg bw intraperitoneally gave negative results in the mouse spot test (Gocke *et al.*, 1983) and, at up to 200 mg/kg intraperitoneally or 400 mg/kg orally, in the rat micronucleus test (Setnikar *et al.*, 1976; Goodman *et al.*, 1977). At five daily intraperitoneal doses of 8 or 40 mg/kg bw, nitrofurantoin did not induce chromosomal aberrations in spermatocytes of mice (Fonatsch, 1977). It also gave negative results in the dominant lethal test in mice after intraperitoneal administration of 16 and 80 mg/kg bw (Epstein *et al.*, 1972) and equivocal results after five daily oral doses of 17.5 mg/kg bw (Setnikar *et al.*, 1976).

(*b*) *Humans*

(i) *Pharmacokinetics*

Nitrofurantoin is readily absorbed from the gastrointestinal tract (Reynolds, 1989). The macrocrystalline form is dissolved and absorbed more slowly and produces lower serum concentrations than the microcrystalline form, and peak concentrations in the urine are achieved more slowy (Cunha, 1988; Reynolds, 1989).

After oral administration of nitrofurantoin at 50 mg to six healthy men, the bioavailability was 94 ± 13% on a full stomach and 87 ± 13% on a fasting stomach (Hoener & Patterson, 1981). About 60% of the nitrofurantoin was bound to plasma proteins. After a 45-min intravenous infusion, the plasma distribution followed an open two-compartment model, with a terminal half-time of approximately 1 h. After oral and intravenous infusion, 34 and 47% of the dose was excreted unchanged in the urine, respectively, and 1.2-1.4% was recovered as the reduced metabolite aminofurantoin.

Nitrofurantoin is reduced to aminofurantoin, thus following pathways similar to those known for other nitrofurans (Hoener & Patterson, 1981). Hydroxylation of the furan ring of nitrofurantoin has also been shown (Olivard *et al.*, 1976).

Recovery of the drug in the urine is related linearly to creatinine clearance (Sachs *et al.*, 1968).

After parenteral administration, nitrofurantoin crosses the human placenta (Perry & Leblanc, 1967; Kobyletzki, 1968).

(ii) *Adverse effects*

In a study of 757 courses of nitrofurantoin in hospitalized patients, the overall frequency of adverse reactions was 9.2%. Toxic reactions constituted 5.1% of adverse effects; the remainder were allergic (Koch-Weser *et al.*, 1971).

The most common gastrointestinal side-effects of nitrofurantoin are nausea, vomiting and anorexia. These symptoms usually occur during the first week of treatment and are dose-related. Abdominal pain, gastrointestinal bleeding and diarrhoea occur less frequently and without a clear dose-response (Koch-Weser *et al.*, 1971; Gleckman *et al.*, 1979).

Pulmonary infiltration may be caused by sensitivity to nitrofurantoin (Israel & Diamond, 1962). Acute pulmonary sensitivity reactions are manifested by fever, chills, cough, dyspnoea, and possible bronchospasm and chest pain associated with eosinophilia (Glueck & Janower, 1969). Subacute pulmonary reactions have been considered to be a separate syndrome (Gleckman *et al.*, 1979; D'Arcy, 1985), developing after one month of treatment with nitrofurantoin, and are characterized by persistent and progressive cough, dyspnoea and fever, together with interstitial pneumonitis (Sollaccio *et al.*, 1966; Sovijärvi *et al.*, 1977). The chronic nitrofurantoin pulmonary reaction is characterized histologically by nonspecific, diffuse interstitial pneumonitis and fibrosis (Rosenow *et al.*, 1968; Ruikka *et al.*, 1971; Castleman, 1974; Holmberg *et al.*, 1980).

Nitrofurantoin has been associated with adverse effects on the liver, including acute hepatocellular and cholestatic injury (Goldstein *et al.*, 1974), as well as rare cases resembling chronic active hepatitis (Klemola *et al.*, 1975; Black *et al.*, 1980; Sharp *et al.*, 1980).

Peripheral polyneuropathy is the most common neurological side-effect, although dizziness, vertigo, diplopia and cerebellar disturbance have also been reported (Graebner *et al.*, 1973).

Haemolytic anaemia is a well-documented complication of nitrofurantoin therapy in patients with glucose-6-phosphate dehydrogenase deficiency (Swanson & Cook, 1977). Haemolysis has also been reported in patients deficient in enolase and glutathione peroxidases (Steinberg *et al.*, 1970; Stefanini, 1972). In addition, there have been case reports of megaloblastic anaemia (Bass, 1963), agranulocytosis (Palva & Lehmola, 1973; Böttiger & Westerholm, 1977) and aplastic anaemia (Böttiger & Westerholm, 1977).

(iii) *Effects on reproduction and prenatal toxicity*

In the Collaborative Perinatal Project, in which drug intake and pregnancy outcome were studied in a series of 50 282 women in 1959-65, 83 women had been exposed to nitrofurantoin during the first trimester of pregnancy. Six malformed

children were born in the exposed group, giving a standardized nonsignificant relative risk of 1.07 (Heinonen *et al.* 1977).

Hailey *et al.* (1983) reported on the use of nitrofurantoin during 91 pregnancies in 81 women in one practice in 1972-80. In 36% of women, treatment was given during the first trimester. In the 91 pregnancies, one fetal death and two malformed babies (all with exposure during the second or third trimester) were observed. There was no significant difference in the incidence of mortality, malformation, prematurity or low birth weight compared with the general population.

In a brief review of the management of urinary-tract infections in pregnancy, it was stated that, in over 5000 pregnancies treated with nitrofurantoin macrocrystals at 100 mg daily for ten days, the treatment did not produce adverse fetal or neonatal effects and there was no recorded case of neonatal haemolytic anaemia (Whalley, 1985).

(iv) *Genetic and related effects*

Urine of 12 patients was collected before and after treatment with nitrofurantoin at 100 mg. Increased mutagenic activity in *S. typhimurium* TA100 was found in samples taken after treatment (Wang *et al.*, 1977).

3.3 Case reports and epidemiological studies of carcinogenicity to humans

A single case report has been published of focal nodular hyperplasia of the liver in association with nitrofurantoin treatment in a six-year-old girl who had been treated for seven months (Anttinen *et al.*, 1982).

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), 1305 persons to whom at least one prescription for nitrofurantoin had been dispensed during 1969-73 were followed for up to 15 years (Selby *et al.*, 1989). Increased risks were noted for cancer of the uterine corpus (six cases observed, 2.1 expected; $p < 0.05$) and for cancer of other female genital organs (three cases observed, 0.3 expected; $p < 0.05$) during follow-up of up to nine years (Friedman & Ury, 1980, 1983), and for cancers of the nervous system [other than brain] (three cases observed, 0.6 expected; $p < 0.05$) during follow-up of up to 15 years (Selby *et al.*, 1989). [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

Nitrofurantoin has been used since 1972 in the treatment of urinary-tract infections.

4.2 Experimental carcinogenicity data

Nitrofurantoin was tested by oral administration to mice in four studies and to rats in three studies and by transplacental administration to mice in one study. Two of the studies in mice, including the transplacental study, were inadequate for evaluation. In one study in mice, an increase in the incidence of ovarian tubular adenomas and benign mixed tumours was observed. In two studies in other strains of mice, no such increase was observed, although in one study there was an increase in the incidence of malignant lymphomas in males. One study in rats was inadequate for evaluation. A further study in female rats demonstrated an increase in the incidence of mammary fibroadenomas. In the third study in rats, although a few rare tumours were observed, there was no significant increase in the incidence of malignant neoplasms.

4.3 Human carcinogenicity data

In a hypothesis-generating cohort study, use of nitrofurantoin was associated with the occurrence of cancers of the female genital tract and nervous system, but these findings could have been due to chance.

4.4 Other relevant data

Use of nitrofurantoin during pregnancy has not been associated with birth defects. The drug has gonadotoxic effects in male and female rats and mice and teratogenic effects in mice at high doses.

In humans, use of nitrofurantoin has been associated with pulmonary fibrosis, hepatocellular injury, aplastic anaemia and other blood dyscrasias.

Nitrofurantoin gave negative results in the mouse spot test and in the rat micronucleus test. It did not induce chromosomal aberrations in male germ cells or dominant lethal effects in mice. It induced DNA strand breaks in rats and mice and sister chromatid exchange and unscheduled DNA synthesis in bone-marrow cells of mice. Nitrofurantoin induced DNA strand breaks in mouse, rat and human cells *in*

vitro and increased the frequency of sister chromatid exchange in Chinese hamster cells but not in human cells *in vitro*. Nitrofurantoin induced chromosomal aberrations in Chinese hamster cells but not in human cells *in vitro*. It did not induce unscheduled DNA synthesis in human fibroblasts or rat hepatocytes *in vitro*. It induced gene mutations in Chinese hamster cells. Nitrofurantoin gave ambiguous results in *Drosophila* in the sex-linked recessive lethal test but positive results in the wing spot test. It gave contradictory results in tests for mitotic gene conversion in *Saccharomyces cerevisiae*. Nitrofurantoin induced differential toxicity in *Escherichia coli*, *Salmonella typhimurium* and *Bacillus subtilis* and mutations in *E. coli* and *S. typhimurium*. (See Appendix 1.)

4.5 Evaluation[1]

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

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

Overall evaluation

Nitrofurantoin *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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