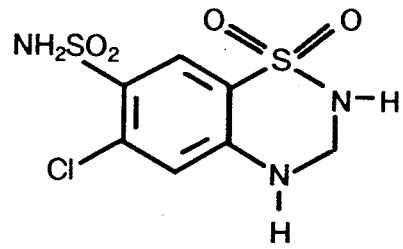
HYDROCHLOROTHIAZIDE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 58-93-5
Chem. Abstr. Name: 2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide
Synonyms: 6-Chloro-3,4-dihydro-7-sulfamoyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide; 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide-3,4-dihydrochlorothiazide; chlorosulfonamidodihydrobenzothiadiazine dioxide; chlorosulthiadil

1.2 Structural and molecular formula and molecular weight



$C_7H_8ClN_3O_4S$ Mol. wt: 297.72

1.3 Chemical and physical properties of the pure substance

From Deppeler (1981), unless otherwise specified

(*a*) *Description*: White, fluffy, microcrystalline powder

(*b*) *Melting-point*: 273-275°C (Windholz, 1983)

(*c*) *Solubility*: Practically insoluble in water; soluble in dilute ammonia and sodium hydroxide; soluble in methanol, ethanol, acetone and acetonitrile

(*d*) *Spectroscopy data*: Infrared, ultraviolet, nuclear magnetic resonance and mass spectra have been reported.

(*e*) *Stability data*: Stable in bulk for five years at room temperature; at extremes of pH in aqueous solution, hydrolysed to formaldehyde and 6-chloro-2,4-disulfamoylaniline

(*f*) *Dissociation constant*: pK_a 7.2, 9.2 (Windholz, 1983)

1.4 Technical products and impurities

Trade names: Apo-Hydro; Aquarius; Atenadon; Bremil; Caturida; Chlorthia; Chlorzide; Cidrex; Cloredema; Delco-Retic; Dichlorosal; Dichlortride; Dichlotride; Diclotride; Didral; Diidrotiazide; Direma; Disalunil; Diu 25; Diucen-H; Diurex; Diursana-H; Dixidrasi; Edemex; Esidrex; Esidrix; Fluvin; Hidrenox; Hidroronol; Hidrosaluretil; Hydril; Hydro-Aquil; Hydro-Diuril; Hydro-MURIL; Hydrosaluric; Hydrothide; Hydro-Z; Hydrozide; Hypothiazide; Idrodiuvis; Idrofluin; Idrolisin; Ivaugan; Jen-diral; Lexor; Loqua; Maschitt; Mietrin; Natrimax; Nefrix; Neo-Codema; Neoflumen; Neo-Flumen; Neo Minzil; Newtolide; Novohydrazide; Oretic; Pantemon; Panurin; Ridaq; Ro-Hydrazide; Salupres; Serapres; SK-Hydrochlorothiazide; Tandiur; Thiaretic; Thiuretic; Urirex; Urodiazin; Urozide; Vetidrex

Hydrochlorothiazide is also contained in numerous multi-ingredient preparations.

Hydrochlorothiazide is available as tablets for oral use (25, 50 or 100 mg) containing calcium phosphate, D & C Yellow #6, gelatin, lactose, magnesium stearate, starch and talc (see IARC, 1987) (Barnhart, 1989).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Hydrochlorothiazide in synthesized by either the reaction of *para*-formaldehyde with 5-chloro-2,4-disulfamoylaniline in nonaqueous media, or the reaction of formaldehyde with 6-chloro-7-sulfamoyl-2*H*-1,2,4-benzothiadiazine-1,1-dioxide in aqueous alkaline solution (Deppeler, 1981). It is synthesized in China, Hungary, India, Italy, Japan, Romania, Switzerland, the UK, the USA and Yugoslavia (Chemical Information Services, 1989-90).

Hydrochlorothiazide has been used as a diuretic and antihypertensive agent since 1957 (Reynolds, 1989). More prescriptions were written for hydrochlorthiazide/triamterene combination than for any other prescription drug product in the USA in 1984 and 1985 (Chappell, 1985), and hydrochlorothiazide was the sixth most frequently prescribed generic drug in 1987 and 1988 in the USA (La Piana Simonsen, 1989). In 1988, this drug was sold in Sweden at a level of 0.14 defined daily doses per 1000 inhabitants (Apoteksbolaget, 1988, 1989). In 1987, it was sold in Finland at a level of 2.06 defined daily doses per 1000 inhabitants (Finnish Committee on Drug Information and Statistics, 1987).

Hydrochlorothiazide is not known to occur as a natural product.

2.2 Use

Hydrochlorothiazide is a thiazide diuretic (Reynolds, 1989). It is used to reduce oedema associated with heart failure, as an antihypertensive agent, and for special indications such as Ménière's disease (Roydhouse, 1974) and reduction of the formation of renal calculi in patients with hypercalciuria (Yendt *et al.*, 1970; Baggio *et al.*, 1986). The daily dose of hydrochlorothiazide in treating oedema is 25-50 mg after an initial dose of twice this amount. The daily dose for children is 2.5 mg/kg bw and that for infants under six months, 3.5 mg/kg bw. The antihypertensive doses of hydrochlorothiazide vary between 25 and 200 mg daily (Reynolds, 1989).

2.3 Analysis

Hydrochlorothiazide can be analysed in urine and plasma by colorimetry, thin-layer chromatography and high-performance liquid chromatography (Sheppard *et al.*, 1960; Redalieu *et al.*, 1978; Suria, 1978; Koopmans *et al.*, 1984; Alton *et al.*, 1986; Fullinfaw *et al.*, 1987; van der Meer & Brown, 1987). Analysis of hydrochlorothiazide in pharmaceutical preparations has also been reported (Cieri, 1988; US Pharmacopieal 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, seven to eight weeks of age, were fed hydrochlorothiazide (> 98% pure) at 0, 2500 or 5000 mg/kg of diet for 103-104 weeks (average daily intake, 280 or 575 mg/kg bw), and all survivors were killed at weeks 113-114. Mean body weights were similar in control and treated mice. Survival in males was: control, 43/50; low-dose, 42/50 and high-dose, 43/50; that in females was: control, 38/50; low-dose, 40/50 and high-dose, 35/50. All animals were necropsied, and samples taken from all major organs, tissues and gross lesions were examined histologically. A significant increase in the incidence of hepatocellular adenomas and of combined adenomas and carcinomas (control, 7/48; low-dose, 10/49; high-dose, 21/50 (p = 0.009, incidental tumour test)) but not of carcinoma alone was observed in males. No increase in the incidence of any other neoplasm was observed (National Toxicology Program, 1989).

Rat: A group of 24 male and 24 female Fischer 344 rats, six to eight weeks of age, were fed hydrochlorothiazide [purity unspecified] at 1000 mg/kg of diet for 104 weeks (total intake: males, 21 g; females, 14 g). A control group of 24 male and 24 female rats remained untreated. Over 70% of the rats survived more than two years, with similar survival rates in all groups. All survivors were killed after 130 weeks; complete necropsies were performed on all animals, and major organs were examined histologically. No difference in overall tumour incidence or in the incidence of tumours at any site was observed between treated and control rats (Lijinsky & Reuber, 1987).

Four groups each of 50 male and 50 female Fischer 344/N rats, seven to eight weeks of age, were fed hydrochlorothiazide (>98% pure) at 0, 250, 500 or 2000 mg/kg of diet for 105-106 weeks (average daily intake, 11, 23 or 89 mg/kg bw), and all survivors were killed at weeks 113-114. Survival was—males: control, 18/50; low-dose, 16/50; mid-dose, 9/50; high-dose, 11/50; females: control, 31/50; low-dose, 25/50; mid-dose, 30/50; high-dose, 27/50. All animals were necropsied, and samples from all major organs, tissues and gross lesions were examined histologically. No increase in either overall tumour incidence or in the incidence of tumours at any site was observed (National Toxicology Program, 1989).

(*b*) *Administration in combination with other compounds*

Rat: In the experiment by Lijinsky and Reuber (1987), described above, three groups each of 24 male and 24 female Fischer 344 rats, six to eight weeks of age, were fed diets containing hydrochlorothiazide [purity unspecified] at 1000 mg/kg, sodium nitrite at 2000 mg/kg or hydrochlorothiazide at 1000 mg/kg plus sodium nitrite at 2000 mg/kg for 104 weeks. Over 70% of the rats survived more than two years, with similar survival rates in all groups. All survivors were killed after 130 weeks; complete necropsies were performed on all animals, and major organs were examined histologically. No difference in overall tumour incidence or in the incidence of tumours at any site was observed between treated and control rats.

3.2 Other relevant data

(*a*) *Experimental systems*

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

No data were available to the Working Group.

(ii) *Toxic effects*

The oral LD_{50} for hydrochlorothiazide in mice was 3080 mg/kg bw (Barnes & Eltherington, 1965).

All 20 dogs receiving hydrochlorothiazide at daily doses of 50-200 mg for up to nine months had enlarged, hyperactive parathyroid glands (Pickleman *et al.*, 1969).

In male (but not female) Syrian golden hamsters receiving hydrochlorothiazide at 1 or 2 mg/kg bw by gavage for six months, increased total cholesterol and high-density lipoprotein cholesterol levels were observed. When a dose of 4 mg/kg bw was administered, a similar increase was seen in animals of each sex (Sarva *et al.*, 1985).

All male and female rats fed diets containing 3.125-50 g/kg (five dose levels) hydrochlorothiazide survived for 15 days. Thymic haemorrhage of slight to moderate severity was observed in animals receiving the highest doses, but no other toxic effect was observed (National Toxicology Program, 1989).

In groups of 24 male and 24 female rats fed hydrochlorotriazide at 1000 mg/kg of diet for two years, the incidence and severity of chronic progressive nephropathy and of lesions secondary to chronic renal disease, polyarteritis and mural thrombosis were increased (Lijinsky & Reuber, 1987).

In a two-year study (see section 3.1), there was a uniform reduction in the body weight of treated rats (male and female) at all doses. Chronic renal disease (cysts of the parenchyma and epithelial hyperplasia of the renal pelvis) was present in all groups of male and female rats, but it was more severe in dosed groups. Secondary signs of chronic renal disease, including parathyroid hyperplasia, mineralization in multiple organs and fibrous osteodystrophy, also occurred at increased frequency in dosed groups. No other lesion in rats appeared to be related to exposure to hydrochlorothiazide. In mice, a two-year exposure had only negligible effects on body weight. No increase in the frequency of non-neoplastic lesions in the kidney, urinary bladder or any other organ was attributed to hydrochlorothiazide administration (National Toxicology Program, 1989).

(iii) *Effects on reproduction and prenatal toxicity*

Hydrochlorothiazide was administered by gavage to pregnant CD rats at 100, 300 or 1000 mg/kg bw per day and to CD-1 mice at 300, 1000 or 3000 mg/kg bw per day on gestational days 6-15. No dose-related fetal toxicity or significant increase in the incidence of malformations was observed (National Toxicology Program, 1989).

(iv) *Genetic and related effects*

Hydrochlorothiozide did not induce reversion in an *arg*$^-$ strain of *Escherichia coli* (Hs30R) (Fujita, 1985). It was not mutagenic to *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system (Waskell, 1978; Andrews *et al.*, 1984). [The Working Group noted that only one concentration was used in both studies.] In strain TA98, but not in TA1535, TA1537 or TA100, a small, reproducible, concentration-dependent increase in the mean number of revertants was observed in the absence, but not in the presence, of an exogenous metabolic system (Mortelmans *et al.*, 1986).

In a spot test, hydrochlorothiazide induced nondisjunction and mitotic crossing-over in *Aspergillus nidulans* (Bignami *et al.*, 1974).

Hydrochlorothiazide did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* either fed or injected with solutions of 10 mg/ml (Valencia *et al.*, 1985).

At concentrations above 500 μg/ml, hydrochlorothiazide produced cytotoxic effects and induced mutations to trifluorothymidine resistance in L5178Y mouse lymphoma cells in the absence of an exogenous metabolic system (National Toxicology Program, 1989). Significant, but not concentration-dependent, increases in the frequency of sister chromatid exchange were observed in Chinese hamster CHO cells in the presence and absence of an exogenous metabolic system (Galloway *et al.*, 1987). Chromosomal aberrations were not found in Chinese hamster lung CHL cells, but polyploidy was observed after 48 h treatment (Ishidate, 1988). Chromosomal aberrations were also not detected in Chinese hamster CHO cells in the presence or absence of an exogenous metabolic system at concentrations of up to 2600 μg/ml (Galloway *et al.*, 1987).

(*b*) *Humans*

(i) *Pharmacokinetics*

The pharmacokinetics of hydrochlorothiazide have been reviewed (Welling, 1986).

Hydrochlorothiazide is incompletely absorbed from the duodenum and upper jejunum (Beermann *et al.*, 1976), and plasma concentrations, peaking at about 2-3 h after intake, are proportional to the dose within the range 25-100 mg (Patel *et al.*, 1984). Administration with food either enhances (Beermann & Groschinsky-Grind, 1978) or reduces (Barbhaiya *et al.*, 1982) the absorption of hydrochlorothiazide, as compared with fasting conditions. The discrepancy is partly attributable to differences in fasting states in these experiments. Food might delay passage through the small intestine; patients with intestinal shunt surgery and accelerated intestinal passage have shown reduced absorption of hydrochlorothiazide (Backman *et al.*, 1979).

Hydrochlorothiazide is concentrated in red blood cells (Beermann *et al.*, 1976; Redalieu *et al.*, 1985). It is excreted almost entirely unchanged in urine; its renal clearance rate (about 300 ml/min) indicates combined glomerular filtration and tubular secretion (Barbhaiya *et al.*, 1982). Its plasma elimination half-time is about 6 h initially but up to 15 h terminally (Patel *et al.*, 1984). In patients with decreased renal function, the plasma half-time of hydrochlorothiazide is prolonged to 20 h (Niemeyer *et al.*, 1983).

Concentrations of hydrochlorothiazide in maternal plasma and umbilical cord plasma were similar (Beermann *et al.*, 1980) and were lower than those in amniotic fluid (Mulley *et al.*, 1978). The drug was detected in the milk of nursing mothers

treated with it, but no measurable concentration was found in nursing infants (detection limit, 20 ng/ml) (Miller *et al.*, 1982).

(ii) *Adverse effects*

Administration of large doses of hydrochlorothiazide often leads to electrolyte imbalance, including hypochloraemic alkalosis, hyponatraemia, hypokalaemia and hypercalcaemia (Porter *et al.*, 1978; Zalin *et al.*, 1984; Bayer *et al.*, 1986; Reynolds, 1989).

Like other thiazide diuretics, hydrochlorotriazide is known to produce metabolic effects, such as hyperglycaemia and glycosuria, in diabetic and other susceptible patients (Flamenbaum, 1983; Freis, 1986). It produces asymptomatic hyperuricaemia in many patients, although actual attacks of gout are not common (Anon., 1987).

Hyperparathyroidism associated with prolonged intake of thiazides, including hydrochlorothiazide, has been reported (Paloyan & Pickleman, 1969; Christensson *et al.*, 1977; Klimiuk *et al.*, 1981).

A number of skin diseases of an allergic and idiosyncratic nature have been reported among patients treated with thiazide diuretics (Ebstein & Wintroub, 1985; Reed *et al.*, 1985; Hardwick & Saxe, 1986).

Interstitial nephritis (Linton *et al.*, 1980; Scully *et al.*, 1983), idiosyncratic pneumonitis (Piper *et al.*, 1983; Parfrey & Herlong, 1984), thrombocytopenia (Eisner & Crowell, 1971), intravascular haemolysis (Beck *et al.*, 1984) and pancreatitis (Cornish *et al.*, 1961) have been reported in patients treated with thiazide diuretics.

(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, 107 women had been exposed to hydrochlorothiazide during the first trimester of pregnancy. There were nine malformed children in the exposed group, giving a nonsignificant standardized relative risk of 1.2 (Heinonen *et al.*, 1977).

(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), 12 799 persons to whom at least one prescription for a thiazide diuretic had been dispensed during 1969-73 were followed up for up to 15 years (Selby *et al.*, 1989). Hydrochlorothiazide was the predominant drug used in this group.

Increased risks were noted for cancer of the prostate (53 cases observed, 38.2 expected; $p < 0.05$) during follow-up of up to seven years (Friedman & Ury, 1980) and for cancers at all sites combined (1209 observed, 1132.9 expected; $p < 0.05$) during follow-up of up to 15 years (Selby *et al.*, 1989). The association with prostatic cancer diminished in later follow-up. [The Working Group noted that prostatic cancer may be diagnosed more readily in patients under more intensive medical care. In addition, as also noted by the authors, since some 12 000 comparisons were made in this hypothesis-generating study, the associations should be verified independently. Data on duration of use were not provided.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Hydrochlorothiazide has been used extensively since 1957 as a diuretic and antihypertensive agent.

4.2 Experimental carcinogenicity data

Hydrochlorothiazide was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats. An increase in the incidence of hepatocellular adenomas was observed in male mice. No increase in the incidence of tumours at any site was observed in two studies in rats.

4.3 Human carcinogenicity data

In one hypothesis-generating study in which many drugs were screened for possible carcinogenicity, associations with hydrochlorothiazide use were observed for cancers of the prostate and of all sites combined, which could be accounted for by chance.

4.4 Other relevant data

One study provided no evidence that use of hydrochlorothiazide in the first trimester of pregnancy is associated with the induction of birth defects. In rats, no teratogenic, embryotoxic or fetotoxic effect was observed.

Hydrochlorothiazide induced gene mutations in mouse lymphoma cells and sister chromatid exchange in Chinese hamster cells. It did not induce chromosomal aberrations in Chinese hamster cells *in vitro* or sex-linked recessive lethal mutations in *Drosophila*. Hydrochlorothiazide induced mitotic recombination and nondis-

junction in *Aspergillus nidulans*. It was not mutagenic to *Salmonella typhimurium* or *Escherichia coli*. (See Appendix 1.)

4.5 Evaluation[1]

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

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

Overall evaluation

Hydrochlorothiazide *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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