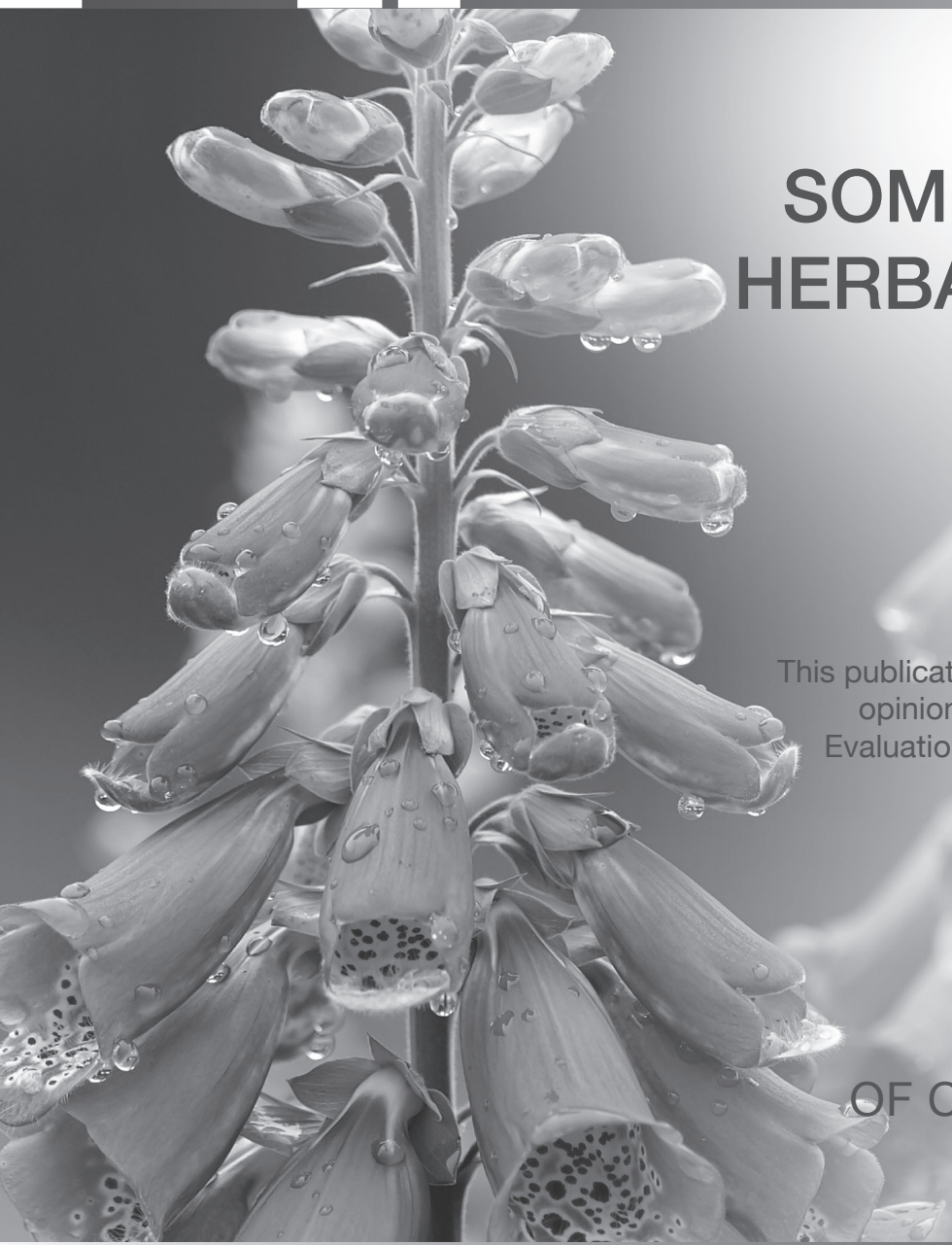
IARC MONOGRAPHS



SOME DRUGS AND HERBAL PRODUCTS

VOLUME 108

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 4–11 June 2013

Lyon, France - 2016

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

HYDROCHLOROTHIAZIDE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 58-93-5 (SciFinder, 2013)

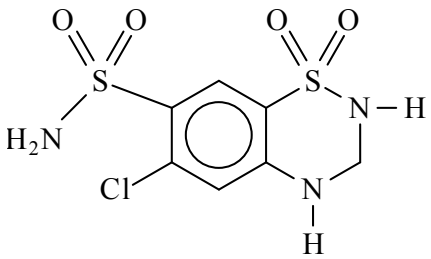
Chem. Abstr. Serv. Name: 2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide (SciFinder, 2013)

IUPAC systematic name: 6-Chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide

Synonyms: Dihydrochlorothiazid; Dihydrochlorothiazide; Dihydrochlorothiazidum; Dihydrochlorurit; Dihydrochlorurite; Dihydroxychlorothiazidum; HCTZ; HCZ; Hydrochlorothiazid; Hydrochlorthiazide (DrugBank, 2013); Hidroclorotiazida; Hydrochlorothiazidum; Chlorsulfonamido-dihydrobenzothiadiazine dioxide; Chlorosulthiadil; 3,4-dihydrochlorothiazide (IPCS, 2013)

WHO International Nonproprietary Name (INN): Hydrochlorothiazidum (WHO, 2006)

1.1.2 Structural and molecular formulae and relative molecular mass



$C_7H_8ClN_3O_4S_2$

Relative molecular mass: 297.74 (O'Neil, 2001)

1.1.3 Chemical and physical properties of the pure substance

Description: A white or almost white, crystalline powder; odourless or almost odourless (WHO, 2006)

Density: 1.693 g/cm^3 (calculated) (Lookchem, 2013)

Melting point: 273–275 °C (O'Neil, 2001)

Spectroscopy data: Infrared, Raman, ultraviolet, proton nuclear magnetic resonance (^{1}H-NMR) and ^{13}C-NMR spectral data have been reported.

Solubility: Very slightly soluble in water (722 mg/L at 25 °C; Deppeler, 1981); soluble in ethanol at ~750 g/L and in acetone (WHO, 2006); soluble in dilute ammonia; freely soluble in sodium hydroxide solution, in

n-butylamine and in dimethylformamide; sparingly soluble in alcohol; insoluble in ether, chloroform and in dilute mineral acids (HSDB, 2013).

Octanol/water partition coefficient (log P): −0.07 (Chemspider, 2013)

Dissociation constant: pK_a = 7.9 ; pK_{a2} = 9.2 (O'Neil, 2001)

1.1.4 Technical products and impurities

(a) Trade names

Acuren; Adelphan; Apo-Hydro; Aquazide; Clorana; Colidur; Colonraitai; Cotrazid; Decazon; Dehydratin; Dehydrazid; Depress; Dichlotride; Dichlozid; Di-Eudrin; Dihydrochl Ozide; Dihydrochlorothiazide; Dihydrodiazid; Disalunil; Disothiazide; Dithiazide; Dithiazide; Diunorm; Diunorm; Diurace; Diural; Diuren; Diurex; Diurezin; Diuzid; Do-Hydro; Drenol; Duberzide; Edepress; Esidrex; Esidrix; H.C.T.; HCT [manufacturer]; Hexazide; Hidroclorotiazida; Hidrochlorotiazid Alkaloid; Hidromed; Hidroronol; Hidrosaluretil; Hidrotiadol; HTZ; Hybozide; Hychlozide; Hydrex; Hydride; Hydrochlorothiazide; Hydrochlorothiazidum Polpharma; Hydroklortiazid Evolan; Hydromed; Hydrozide; Hypodehydra; Hypothiazid; Hytaz; Hyzide; Keshiau; Klorzide; Koliside; Locoid; Lonpra; Microzide; Monozid; Nefrix; Newtolide; Nisidrex; Nor-Tiazida; Oretic; Ridaq; Rofucal; Tandiur; Tiazid; Urilzid; Xenia (MicroMedex, 2013).

(b) Impurities

Some impurities are described in the European Pharmacopoeia (2005):

- Chlorothiazide (active drug rarely used as an alternative to hydrochlorothiazide)
- 4-Amino-6-chlorobenzene-1,3-disulfonamide (salamide)
- 6-Chloro-*N*-[(6-chloro-7-sulfamoyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazin-4-yl 1,1-dioxide)methyl]-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

1.2 Analysis

An overview of selected analytical methods is presented in Table 1.1.

1.3 Production and use

1.3.1 Production process

Hydrochlorothiazide is 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).

1.3.2 Use

(a) Indications

Hydrochlorothiazide is a thiazide-type diuretic chiefly used as an antihypertension agent for the control of elevated blood pressure (Table 1.2). It is often combined with other agents in the treatment of hypertension, either through separate prescriptions for hydrochlorothiazide and the other agents, or through the use of combination products in which a single tablet contains hydrochlorothiazide plus one other antihypertensive medication (more rarely, two other agents).

In the USA, hydrochlorothiazide is indicated for "the management of hypertension either as the sole therapeutic agent or in combination with other antihypertensives" and is recommended as first-line medication (Chobanian *et al.*, 2003). The Food and Drug Administration

Table 1.1 Analytical methods for hydrochlorothiazide

Sample matrix	Sample preparation	Analytical method	Detection limit	Reference
Compendial methods				
Assay	–	Potentiometry Titrant: 0.1 M TBAH Reference electrode: calomel or silver–silver chloride Indicator electrode: glass electrode 1 mL of 0.1 M TBAH is equivalent to 0.01488 g of HCTZ	–	Indian Pharmacopoeia (2010)
Assay for HCTZ tablets	–	UV-visible spectroscopy wavelength: 273 nm	–	Indian Pharmacopoeia (2010)
Assay for HCTZ tablets	–	HPLC column: C_{18} Mobile phase: monobasic sodium phosphate and acetonitrile (9 : 1) pH 3.0 ± 0.1 Flow rate: 2 mL/min	–	US Pharmacopeia (2007)
Non-compendial methods				
Human plasma	Addition of internal standard (clortalidone) and MTBE, centrifugation, addition of solvent to organic phase, evaporation and reconstitution in acetonitrile and water (1 : 1, v/v)	HPLC–tandem mass spectrometry Column: C_{18} Mobile phase: acetonitrile and water (80 : 20, v/v) SRM transition: 296.10 *m/z*, 204.85 *m/z*	5 ng/mL (LLOQ) Linearity: 5–400 ng/mL	Sousa *et al.* (2009)
Human urine	Mix urine samples with deionized water, centrifuge	HPLC–narrow bore chromatography Column: C_{18} Mobile phase: acetic acid and acetonitrile (93 : 7) pH 3 Wavelength: 272 nm Flow rate: 0.30 mL/min	1 µg/mL (LOD) Linearity: 2–50 µg/mL	Farthing *et al.* (1998)
Human serum	Gel filtration of the sera on Sephadex G-15, extraction of the protein-free fraction of the effluent with ethyl acetate	HPLC Column: C_{18} (Spherisorb ODS) Mobile phase: 15% methanol in water	50 ng/mL (LOD)	Christophersen *et al.* (1977)
Rat plasma	To plasma add internal standard (HFTZ), extraction with MTBE	LC–ESI–MS Column: C_8 Mobile phase: distilled water and acetonitrile (85 : 15) Negative ionization mode	Linearity: 4–1000 ng/mL Accuracy: 100.8–113.1% Precision: 0.28–16.4%	Takubo *et al.* (2004)

Table 1.1 (continued)

Sample matrix	Sample preparation	Analytical method	Detection limit	Reference
Human plasma, simultaneous determination of HCTZ and captopril	Derivatization with 2,4-dibromoacetophenone (pBPB) to form captopril-pBPB adduct. Extraction of HCTZ and derivatized captopril with ether and dichloromethane	Reverse phase HPLC Column: C_{18} Mobile phase: acetonitrile, trifluoroacetic acid and water (gradient elution) Flow rate:1.2 mL/min	3.3 ng/mL (LOQ)	Huang *et al.* (2006)
Human plasma, simultaneous quantitation of HCTZ and telmisartan	Liquid–liquid extraction with diethyl ether and dichloromethane (60 : 40)	LC–MS Column: C_8 Mobile phase: acetonitrile, 10 mM ammonium acetate and formic acid (gradient elution) Flow rate: 1.2 mL/min SRM transition: 295.9 *m/z* → 268.9 *m/z* Negative ionization mode	Linearity: 1.00–600 ng/mL	Yan *et al.* (2008)
Human blood and plasma	Addition of the internal standard, benzene extraction, extraction with ethyl acetate, back-extraction into NH_4OH, adjustment to pH 3.7 and extraction with ethyl acetate, evaporation, dissolution of the residue in trimethylanilinium hydroxide in methanol	GLC Column: glass U-tube Carrier gas: argon : methane (95 : 5) Flow rate: 60 mL/min Detector: electron capture detector	0.05 µg/mL (sensitivity)	Vandenheuvel *et al.* (1975)
In tablets	Dissolve drug in 0.02 M NaOH, dilute with Britton–Robinson buffer pH 3.3	Electrochemical study Electrode: glass carbon electrode pH 3.3 Oxidation potential: + 1040 mV	5.0 ng/mL (LOD)	Abdel Razak (2004)
In urine	Centrifugation at 4000 g/mL spiked with HCTZ and diluted with Britton–Robinson buffer pH 3.3	Electrochemical study Electrode: glass carbon electrode pH 3.3 Oxidation potential: + 1040 mV	14 ng/mL	Abdel Razak (2004)
In pharmaceutical formulations	Solution of HCTZ in acetone	Diffuse reflectance spectroscopy: Whatman 42 filter paper as the solid support Solvents: acetone and methanol (HPLC grade); PDAC used for spot reaction with HCTZ	1.32×10^{-2} mol/L (LOD) Linearity: 3.36×10^{-2} to 1.01×10^{-1} mol/L	Gotardo *et al.* (2005)

GLC, gas-liquid chromatography; HCTZ, hydrochlorothiazide; HFTZ, hydrofluorothiazide; HPLC, high-performance liquid chromatography; LC-MS, liquid chromatography mass spectroscopy; LC–ESI–MS, liquid chromatography–electrospray ionization–mass spectrometry; LOD, limit of detection; LLOQ, lower limit of quantification; LOQ, limit of quantification; MTBE, methyl *tert*-butyl ether; PDAC, *para*-dimethylamino cinnamaldehyde; SRM, single reaction monitoring; TBAH, tetrabutylammoniumhydroxide; UV, ultraviolet; v/v, volume per volume

Table 1.2 Most commonly reported clinical indications for hydrochlorothiazide in the USA, 2012

Diagnosis[a]	ICD-9 code	Drug uses (in thousands)	Percentage of total
Essential hypertension, NOS	401.90	21 194	86.9
Hypertensive heart disease, other	402.90	713	2.9
Chronic ischaemic disease, unspecified, with hypertension	414.50	324	1.3
Hypertension, benign	401.10	187	0.8
Surgery after heart disease	V67.03	153	0.6
Hypertensive renal disease	403.90	136	0.6
Oedema, NOS	782.30	122	0.5
Cerebrovascular accident	436.00	86	0.4
Metabolic/insulin resistance syndrome	277.70	82	0.3
All other diagnoses	–	1 332	5.5
Total with reported diagnoses	–	24 383	100

[a] No diagnosis was stated for 0.2% of drug uses.
NOS, not otherwise specified
From IMS Health (2012a)

has approved hydrochlorothiazide alone, and thirty-four combinations containing two agents, and four combinations containing three agents, although not all of these forms were currently available (FDA, 2013). The most common drugs combined with hydrochlorothiazide are triamterene (see *Monograph* on triamterene in this volume), lisinopril, losartan, and valsartan (IMS Health, 2012a).

The European Medicines Agency indication for hydrochlorothiazide is "for treatment of hypertension". Labelling includes use for hypertension and oedema for combination drugs containing hydrochlorothiazide and another diuretic agent. Hydrochlorothiazide is a recommended drug in Europe (Mansia *et al.*, 2007, 2009). Although hydrochlorothiazide is a registered product, it is generally available only in combination products. The European Union listed nineteen combination products containing hydrochlorothiazide and one other drug, and two containing two other agents, although not all are currently in use (eMC, 2013).

(b) Dosage

Hydrochlorothiazide alone (as sold in the USA) is available in doses of 12.5 mg, 25 mg, 50 mg, and 100 mg. In combination with other pharmaceuticals, the dose of hydrochlorothiazide is generally 12.5 mg or 25 mg (eMC, 2013; MicroMedex, 2013).

When used as a single agent tablet in the USA in 2011–12, hydrochlorothiazide was most frequently used at a dose of 25 mg (69%), followed by 12.5 mg (25%) with higher doses used infrequently (5%). In combination products, a hydrochlorothiazide dosage of 12.5 mg is most common (52%), followed by 25 mg (31%) then 37.5 mg (15%). Both alone and in combination products, once-per-day dosing predominates (> 90%) with twice-per-day and less-than-daily (e.g. every second day) dosing being less common. Overall, the mean daily dosage among patients reported to be taking hydrochlorothiazide is 22 mg per day (IMS Health, 2012a).

(c) Trends in use

Thiazide diuretics, including hydrochlorothiazide, are among the most frequently used antihypertension agents in the USA and western Europe, accounting for roughly 30%

of medications prescribed to patients with high blood pressure (Wang *et al.*, 2007). Other data confirmed that 25–30% of USA patients with hypertension were taking thiazide diuretics in 2009–2010 (Gu *et al.*, 2012). The use of hydrochlorothiazide increased modestly in the mid-2000s (Stafford *et al.*, 2006; Gu *et al.*, 2012) after publication of the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT, 2002; Cushman *et al.*, 2002), which showed reasonable equivalence between chlorthalidone (a thiazide-related diuretic), amlodipine, and lisinopril. Reported uses of hydrochlorothiazide (alone or in combination products) at visits to physicians in the USA then decreased, from 28.9 million uses in 2008 to 24.3 million in 2012. Approximately 10 million patients in the USA were reported to be exposed to hydrochlorothiazide in 2012 (IMS Health, 2012a). Prescriptions containing hydrochlorothiazide dispensed in the USA in 2012 amounted to 126.5 million, a slight decrease from 136.5 million prescriptions in 2008 (IMS Health, 2012b; of these, 48.0 million prescriptions were dispensed for hydrochlorothiazide as a single-agent product (38% of the total for hydrochlorothiazide). Overall, these two data sources suggested modest declines in use over the past decade.

Total worldwide sales of hydrochlorothiazide in 2012 were US$ 10.1 billion. Sales were highest in the USA at US$ 3.4 billion, followed by Germany (US$ 0.9 billion), Japan (US$ 0.7 billion), Italy (US$ 0.6 billion), France (US$ 0.5 billion), Brazil (US$ 0.4 billion), Spain (US$ 0.4 billion), India (US$ 0.15 billion), and China (US$ 0.1 billion). The generally lower sales outside of the USA (even when adjusted for population size) reflect the greater use of other thiazide and thiazide-type diuretics in other countries (IMS Health, 2012c).

[Based on data from Wang *et al.* (2007) and Kuehlein *et al.* (2011), the Working Group calculated that 44% of patients treated for hypertension in Germany were treated with hydrochlorothiazide. This suggested that hydrochlorothiazide represented about 25% of all drugs used for hypertension in this country. These results were very consistent with previous reports that diuretics represented 39% of all drugs mentioned for German patients with hypertension, and compendium information suggesting that hydrochlorothiazide was not generally available on its own, but rather as a combination product.]

1.4 Occurrence and exposure

Human exposure to hydrochlorothiazide is largely limited to use as a medication. While occupational exposure in manufacturing is likely to occur, no specific studies on hydrochlorothiazide as an agent in occupational or environmental exposure were identified by the Working Group.

1.5 Regulations and guidelines

Hydrochlorothiazide has been widely approved by drug regulatory agencies around the world. In the USA, it was approved by the Food and Drug Administration (FDA, 2013) in 1959. The Working Group did not identify extraordinary regulatory restrictions on use of hydrochlorothiazide as a medication, or regulations on environmental exposure.

2. Cancer in Humans

Hydrochlorothiazide is a diuretic in a class of thiazide compounds primarily used to treat hypertension, but also oedema and congestive heart failure. In addition to diuretic effects on the kidney, hydrochlorothiazide has photosensitizing properties, enhancing skin sensitivity to sunlight exposure.

Epidemiological studies have investigated associations with use of hydrochlorothiazide using pharmacy information in pre-paid health plans and data from national databases linking with physician and/or cancer registry information. Some studies evaluated thiazides as a class of drugs either through prescription records or self-reported use. The types of cancers investigated or observed in these studies included those related to exposure to sunlight (e.g. lip or cutaneous malignancies), and those of the kidney (e.g. renal cell carcinoma), with a few reports of other malignancies (e.g. cancers of the prostate, colon, breast, and endometrium). See Table 2.1 and Table 2.2.

2.1 Cancers of the lip and skin

Using data from 1994 to 2006 from the Kaiser Permanente Medical Care Program in northern California, USA, Friedman *et al.* (2009) screened for drugs potentially related to cancer occurrence by analysing cancer cases and controls matched on age (same year), sex, year of starting drug coverage, and index date (matched to the case's date of diagnosis). The analysis considered the potentially confounding effects of HIV positivity, and other medical conditions. Elevated risks were observed for cancers of the lip (odds ratio, OR, 2.29; 95% CI, 1.84–2.86) and all other types of cancer of the skin combined, including Merkel cell, malignant fibrous histiocytoma, dermatofibrosarcoma, skin appendage carcinoma and other rarer types (OR, 1.56; 95% CI, 1.20–2.01) in relation to three or more prescriptions of hydrochlorothiazide at least 2 years before diagnosis. No association was observed with cutaneous melanoma or other cancers. [Many comparisons were made. Risk estimates were only provided if they indicated an association with an odds ratio > 1.50 with three or more prescription with a 2-year lag, $P < 0.01$ for difference from odds ratio 1.00, or a higher odds ratio for three or more prescriptions compared with one prescription. Limitations further included the heterogeneity of "other skin cancers" and inability to examine basal cell and squamous cell skin cancers. Also, information was lacking to evaluate the potential confounding or effect modification by factors related to sun exposure. For cancers of the lip and other sites, the results referred to hydrochlorothiazide in combination with other drugs. Since computerized pharmacy records only began in 1994, only a limited latency period could be observed.]

On the basis of the findings from Friedman *et al.* (2009), a similarly designed nested case–control study on cancer of the lip was carried out from 1994 to 2008; the study included 712 cases (of which 97.2% were squamous cell carcinomas of the lip) and 22 904 non-Hispanic, white controls (Friedman *et al.*, 2012). An increased odds ratio for cancer of the lip was observed for people having three or more prescriptions of any medicine containing hydrochlorothiazide (OR, 2.19; 95% CI, 1.74–2.76) or exclusively hydrochlorothiazide (OR, 2.03; 95% CI, 1.23–3.36) at least 2 years before the reference date. Odds ratios were higher with longer duration of prescriptions. [A strength of this study was the large sample size that allowed them to look at hydrochlorothiazide alone; however, there were no data on potentially modifying or confounding factors, including factors related to sun exposure. The definition of cancer of the lip presumably used the definition provided by the Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute, USA.]

In a population-based nested case–control study from North Jutland, Denmark, diagnoses of melanoma, squamous cell carcinoma, and basal cell carcinoma from 1989 to 2003 were identified through the Danish cancer registry, which includes non-melanoma as well as melanoma of the skin (Jensen *et al.*, 2008). Four controls per case were selected from the Danish Civil Registration System, matched on age (exact), sex, and area of residence. Prescriptions

Table 2.1 Case–control studies of thiazides (including hydrochlorothiazide) and cancer

Reference Location; period	Total cases Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Friedman *et al.* (2009) Northern California, USA; August 1994–December 2006	NR	KPMCP subscribers	KPMCP computerized prescription records		HCTZ use, including combinations, ≥ 3 dispensings, 2-yr lag[a]			Controls matched on sex, year of birth, and year of starting drug coverage
	NR			Kidney (renal pelvis)	No		1.00 (ref.)	
					Yes	537	1.71 (1.54–1.91)	Nested case–control study of 10 controls to each case identified by the KPMCP cancer registry
				Lip	No		1.00 (ref.)	Uncertainty as to whether the association with kidney cancer was due to hypertension or the drug
					Yes	147	2.29 (1.84–2.86)	Lung cancer only weakly related to lip cancer, making confounding by smoking less likely to be an explanation
				Skin (other than lip)	No		1.00 (ref.)	Other types of cancer of the skin included: 35 Merkel cell carcinoma, 14 malignant fibrous histiocytoma, 8 dermatofibrosarcoma, 7 skin appendage carcinoma, 5 or fewer of 14 other rarer types
					Yes	95	1.56 (1.20–2.01)	

Table 2.1 (continued)

Reference Location; period	Total cases Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Friedman *et al.* (2012) Northern California, USA; 1994–2008	712 22 904 controls	Subscribers to KPMCP	KPMCP computerized prescription records	Lip	HCTZ use, including combinations, ≥ 3 dispensings, 2-yr lag[a]			Matched on age, sex, year of cohort entry. Adjusted for cigarette smoking Non-Hispanic whites only; age, ≥ 30 yr; excludes transplant recipients and HIV-positive; 3 : 1, men : women
					HCTZ prescriptions[b]	103		
					No HCTZ prescriptions		1.00 (ref.)	
					≥ 3 HCTZ prescriptions		2.19 (1.74–2.76)	No stratum-specific numbers provided, just the overall number of cases prescribed HCTZ alone, only and with triamterene
					HCTZ prescriptions only[a]	19		
					No HCTZ prescriptions		1.0 (ref.)	
					≥ 3 HCTZ prescriptions		2.03 (1.23–3.36)	
					Years of supply:			
					HCTZ:[b]	103		
					< 1 yr		0.98 (0.66–1.45)	
					1 to < 5 yr		2.03 (1.54–2.68)	
					≥ 5 yr		4.22 (2.82–6.31)	
					HCTZ-triamterene:[b]	71		
					< 1 yr		0.91 (0.60–1.39)	
					1 to < 5 yr		1.87 (1.37–2.57)	
					≥ 5 yr		2.82 (1.74–4.55)	

Table 2.1 (continued)

Reference Location; period	Total cases Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Jensen *et al.* (2008) North Jutland County, Denmark; 1989–2003	5964 BCC, 1129 SCC, 1151 MM 32 412 controls	Population	North Jutland County's prescription database	Skin (BCC, SCC, MM)	HCTZ prescriptions before diagnosis			Chronic medical conditions, previous use of oral glucocorticoids, prescriptions for other photosensitizing diuretics
					MM:			
					None		1.00 (ref.)	
					Any	98	1.32 (1.03–1.70)	Sparse data for HCTZ only (n = 13 cases); no association with MM in this limited group
					Prescriptions > 1 yr since diagnosis		1.30 (0.99–1.71)	
					Prescriptions > 5 yr since diagnosis		1.24 (0.86–1.78)	
					Linear per 10 000 mg		0.99 (0.95–1.03)	
					SCC:			
					None		1.00 (ref.)	
					Any	159	1.58 (1.29–1.93)	Sparse data for HCTZ only (n = 5 cases); no clear association with SCC in this limited group
					Prescriptions > 1 yr since diagnosis		1.67 (1.36–2.07)	
					Prescriptions > 5 yr since diagnosis		1.92 (1.46–2.54)	
					Linear per 10 000 mg		1.03 (1.01–1.06)	
					BCC:			
					None		1.00 (ref.)	
					Any	542	1.05 (0.95–1.16)	Wider CIs for HCTZ only (n = 84 cases); no clear association with BCC
					Prescriptions > 1 yr since diagnosis		1.05 (0.94–1.17)	
					Prescriptions > 5 yr since diagnosis		1.10 (0.95–1.26)	
					Linear per 10 000 mg		1.02 (1.00–1.03)	

Table 2.1 (continued)

Reference Location; period	Total cases Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Robinson *et al.* (2013) New Hampshire, USA; 1993–2009	1637 SCC, 1605 BCC 1906 controls	Population	Personal interview	Skin (BCC, SCC)	Thiazides (diuretics)	239		Age, sex, number of previous episodes of painful sunburn OR for photosensitizing cardiovascular drugs (mainly thiazides), 1.3 (95% CI, 1.0–1.6)
					SCC		1.0 (ref.)	OR restricted to HCTZ was similar
							1.3 (0.7–2.4)	
					BCC		"No association"	
de Vries *et al.* (2012) Multicentre (Finland, Germany, Greece, Italy, Malta, Poland, Scotland and Spain)	1371 (602 BCC; 409 SCC; 360 CMM) 1550 controls	Hospital (same dermatology outpatient clinics and hospital departments as the cases)	Questionnaire	Skin (BCC, SCC, CMM)	Thiazide (bendroflumethiazide)			Age, sex, phototype, and country Study period not reported. Age- and sex-matched controls
					CMM	33	1.22 (0.77–1.93)	
					BCC	94	1.27 (0.92–1.75)	
					SCC	99	1.66 (1.16–2.37)	
Hiatt *et al.* (1994) Northern California, USA; 1964–89	257 (167 men, 90 women) 257 controls (167 men, 90 women)	Subscribers to KPMCP	KPMCP prescription records and chart review	Kidney (renal cell carcinoma)	Thiazide, ever-use			History of smoking, BMI, hypertension, history of kidney infection at check-up ORs were highest for the category of longest time since first use, duration of use, number of mentions, and grams, but trends were not statistically significant
					Men:			
					No		1.0 (ref.)	
					Yes		1.2 (0.6–2.1)	
					Women:			
					No		1.0 (ref.)	
					Yes		4.0 (1.5–10.8)	
Stanford *et al.* (1986) USA (BCDDP); 1973–7	1362	Population	Home interview	Breast	Thiazide, ever-use	167	1.22 (0.9–1.6)	Age at diagnosis Exposure information for antihypertensive and oedema medications was truncated at the time of diagnosis for cases or at an equivalent time for controls

Table 2.1 (continued)

Reference Location; period	Total cases Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Li *et al.* (2003) Washington state, USA; April 1997–May 1999	975 1007 controls	Population (CMS list)	In-person interview	Breast	Thiazides Ever-use 6 mo to 5 yr > 5 yr	 246 81 159	 1.4 (1.1–1.8) 1.5 (1.1–2.2) 1.3 (1.0–1.7)	Age Of 1210 eligible cases identified, 975 women (80.6%) were interviewed (14% refused, 4% died, 1% moved away, 1% refused contact with patients). Of the 1365 eligible women who were selected as controls, 1007 women (73.8%) were interviewed (22% refused, 2% died, 2% moved away, 1% not located)
Fortuny *et al.* (2009) New Jersey, USA; 2001–5	469 467 controls	Population	Personal interview	Endometrium	Thiazides No Yes Duration of use: < 3 yr 3–6 yr > 6 yr *P* (trend test)	 369 100 28 23 48	 1.0 (ref.) 1.8 (1.1–3.0) 1.6 (0.8–3.5) 1.2 (0.6–2.8) 2.4 (1.2–4.8) 0.39	Adjusted for age (linear spline), BMI (four categories), demographic factors (education, race), other estrogen-related variables (menarche, hormone therapy, oral contraceptives, age at menopause, parity), smoking, family history of endometrial cancer, plus all other variables included in table Three methods were used to locate controls (random-digit dialling for women aged < 65 yr, CMS lists for women aged ≥ 65 yr, area sampling for women aged ≥ 55 yr)

Table 2.1 (continued)

Reference Location; period	Total cases Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Hallas *et al.* (2012) Denmark; 2000–5	149 417 597 668 controls	Population (Danish cancer registry, Danish national registry of patients, prescription database of the Danish Medicines Agency, and Danish person registry)	Prescription records (database of the Danish Medicines Agency)	Any cancer	Thiazides All malignancies	11 509	1.25 (1.22–1.28)	Prior discharge diagnosis of COPD or inflammatory bowel disease, modified Charlson index that contains 19 categories of comorbidity Four controls matched by age and sex were selected for each case by a risk-set sampling. For all drug classes, those exposed who had taken at least 1000 defined daily doses during the past 5 yr before the index date were considered

[a] Users of other drugs excluded

[b] All use of drug, regardless of other drugs dispensed

BCDDP, Breast Cancer Detection Demonstration Project; BCC, basal cell carcinoma; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CMM, cutaneous malignant melanoma; CMS, Centers for Medicare & Medicaid Services; HCTZ, hydrochlorothiazide; KPMCP, Kaiser Permanente Medical Care Program; mo, month; MM, malignant melanoma; NR, not reported; ref., reference; RR, relative risk; SCC, squamous cell carcinoma; yr, year

Table 2.2 Cohort studies of thiazides (including hydrochlorothiazide) and cancer

Reference Location; period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates Comments
cited in Friedman et al. (2009) USA; 1969–2002	NR	KPMCP computerized prescription records	Kidney	Thiazide use Any use	 55	SMR[a] 1.36 (1.03–1.77)	Limited details on study design. Limited data on potential confounding factors
Ruiter et al. (2010) The Netherlands; 1986–2007	10 692 with no prescriptions for diuretics before April 1991	Computerized pharmacy records	Skin (BCC)	Thiazide use Never used Ever used Days of use: < 94 94–524 524–1646 > 1646	 385 137 34 35 34 34	Hazard ratio 1.0 (ref.) 1.0 (0.95–1.05) 1.02 (0.72–1.45) 0.98 (0.69–1.39) 0.86 (0.60–1.22) 1.10 (0.77–1.58)	Age, sex, smoking, tendency to sunburn, residence in a country with high ambient UV radiation, hair and eye colour, other photosensitizing drugs Cases identified from general practitioners and linkage with national cancer registry. Unclear how many BCC cases may have been missed
Flaherty et al. (2005) United States Nurses' Health Study, USA; 1980–2000; and HPFS, USA; 1998	118 191 women and 48 953 men	Self-report in 1980, then every 2 yr	Kidney (renal cell carcinoma)	Thiazide use Current use in 1980, women Current use in 1986, men 	 22 22 20 20	 1.5 (1.0–2.4) 1.4 (0.9–2.3) 1.5 (0.9–2.5) 0.8 (0.5–1.5)	Limited exposure information, hypertension an independent risk factor Age-adjusted Age, BMI, hypertension Age-adjusted Age, BMI, hypertension
Friedman & Ury (1980) Northern California, USA; 1969–76	143 574 outpatients with at least one prescription filled in 1969–73	KPMCP computerized prescription records	All cancers, prostate	Thiazides Prostate cancer *P* for trend All cancers *P* for trend	 53 585 	SMR 1.4 < 0.05 1.1 NS	Age-, sex-standardized SMR based on expected rates from the 3rd National Cancer Survey in the San Francisco Bay Area. Drugs not specifically HCTZ
van den Eeden & Friedman (1995) San Francisco, USA; 1969–88	143 574	KPMCP prescription records	All cancers (56 cancer sites) Gall bladder	Thiazides	1464 16	SMR 1.07 (1984) SMR 1.02 (1988) SMR 1.8 ($P < 0.05$)	

Table 2.2 (continued)

Reference Location; period	Total No. of subjects	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates Comments
Tenenbaum et al. (2001) Tel Aviv, Israel; 1992–6	14 166 patients with previous myocardial infarction and/ or stable angina syndrome, screened for participation in BIP study (2153 on diuretics; 375 on HCTZ alone; 199 on amiloride/ HCTZ combination)	Derived from intake examination [unclear from paper]	All cancers, colon	All cancers: No diuretics HCTZ HCTZ/ Amiloride Colon cancer: No diuretics HCTZ Amiloride/ HCTZ	 622 29 16 73 5 4	Hazard ratio 1.00 (ref.) 1.41 (0.97–2.05) 1.45 (0.88–2.38) Hazard ratio 1.00 (ref.) 2.12 (0.85–5.26) 3.15 (1.15–8.65)	Significant covariates were included: age, sex, smoking, and triglycerides No information available on duration or doses of drugs administered

[a] HCTZ not distinguished from other thiazides in previous screenings in a smaller cohort, but elevated risk of kidney cancer detected for thiazides as a group.

BCC, basal cell carcinoma; BIP, Bezafibrate Infarction Prevention; HCTZ, hydrochlorothiazide; HPFS, Health Professionals Follow-up Study; KPMCP, Kaiser Permanente Medical Care Program; NR, not reported; NS, not significant; ref., reference; SMR, standardized morbidity ratio; UV, ultraviolet; yr, year

for diuretics were obtained from a database of ambulatory patient prescriptions that began in 1989 and had full coverage of the population in 1991. Taking into account history of chronic disease, prescriptions for oral glucocorticoids and other photosensitizing diuretics, elevated odds ratios were found for squamous cell carcinoma (OR, 1.58; 95% CI, 1.29–1.93) and melanoma (OR, 1.32; 95% CI, 1.03–1.70) in relation to prescriptions for hydrochlorothiazide. A weak association was observed for basal cell carcinoma (OR, 1.05; 95% CI, 0.95–1.16). For squamous cell carcinoma, the odds ratios increased linearly with increasing total dose of prescriptions; the dose trend was weak for basal cell carcinoma, and was not present for melanoma. Additionally, for squamous cell carcinoma, the association was stronger, with a longer lag period from time of prescription to diagnosis. A sensitivity analysis indicated that underascertainment of skin-cancer diagnosis could have led to an underestimate of risk. [A limitation of this study was that it relied on data from medical records and on prescriptions, and thus was not able to assess the potential confounding or modifying effects of factors related to sun exposure. Additionally, hydrochlorothiazide was frequently given with amiloride, and there were too few subjects to evaluate the effects of therapy with hydrochlorothiazide only.]

In a prospective cohort study from the Netherlands, Ruiter *et al.* (2010) used computerized outpatient pharmacy records to assess the relation between thiazide use and basal cell carcinoma. The analysis included 10 692 individuals, largely Caucasian, with no diuretic prescriptions before April 1991. Basal cell carcinomas were identified by general practitioners and linkage with the national cancer registry for 1986 to 2007. After adjustment for multiple potentially confounding factors, no excess risk of basal cell carcinoma was observed with either cumulative duration of use or average grams of thiazide prescription (Ruiter *et al.*, 2010). [It was uncertain whether complete ascertainment of basal cell carcinoma was achieved.]

A population-based case–control study of cases of basal cell carcinoma (n = 1605) and squamous cell carcinoma (n = 1637) and controls that were frequency-matched on age and sex (n = 1906) from New Hampshire, USA, included self-reported use of photosensitizing drugs such as hydrochlorothiazide (Robinson *et al.*, 2013). Elevated odds ratios for squamous cell carcinoma of the skin were observed for reported use of photosensitizing cardiovascular drugs (the majority of which were thiazides) (OR, 1.3; 95% CI, 1.0–1.6), and specifically for thiazides (OR, 1.3; 95% CI, 0.7–2.4); the manuscript indicated that the odds ratio for hydrochlorothiazide was "similar" [which was not surprising since hydrochlorothiazide comprised the majority of the thiazides sold in the USA]. Multiple potentially confounding factors were considered in the analysis, including risk factors related to sun exposure, and history of cigarette smoking. No associations were observed with use of thiazides and basal cell carcinoma. [Limitations of this study were the reliance on self-reported drug use information, lack of statistical power to evaluate effect modification by sunlight-related factors, and failure to report the risk estimate for hydrochlorothiazide.]

A multicentre, hospital-based study of cancer of the skin carried out in Europe (Finland, Germany, Greece, Italy, Malta, Poland, Scotland, and Spain) examined thiazide use determined through questionnaires completed partly by the participant and partly by a dermatology department. The study included 409 cases of squamous cell carcinoma, 602 cases of basal cell carcinoma, 360 cases of cutaneous malignant melanoma, and 1550 controls. Cases were consecutive patients, recently diagnosed (within 3 months of study entry), aged 18 years or older, from one of the participating dermatology practices. Controls were patients visiting the hospital clinics for reasons other than cancer of the skin

and were frequency-matched to cases on age (as far as possible in 5-year strata) and sex. Cases and controls were excluded if they were unable to complete the questionnaire, did not agree to take part, had Fitzpatrick skin types V–VI, had ever received phototherapy, or had photoallergies or lupus erythematosus. A minimum of 3 months, daily intake of self-reported thiazide (bendroflumethiazide) was associated with an odds ratio of 1.66 (95% CI, 1.16–2.37) for squamous cell carcinoma, an odds ratio of 1.27 (95% CI, 0.92–1.75) for basal cell carcinoma, and an odds ratio of 1.22 (95% CI, 0.77–1.93) for cutaneous melanoma (de Vries *et al.*, 2012).

2.2 Renal cell carcinoma

A standardized morbidity ratio (SMR) analysis was conducted of outpatients enrolled in the Kaiser Permanente Medical Care Program with at least one prescription for thiazide filled between 1969–1973 who were followed for cancer until 2002 A total of 55 observed versus 40.34 expected cancers of the kidney were observed among those with thiazide prescriptions (SMR, 1.36; 95% CI, 1.03–1.77) (Friedman *et al.*, 2009). [Limited details on the study design were provided, and there were limited data available on potentially confounding or modifying factors.]

In the nested case–control analyses of data from the Kaiser Permanente Medical Care Program from 1994–2006 conducted by Friedman *et al.* (2009), an increased risk of cancer of the renal pelvis (OR, 1.71; 95% CI, 1.54–1.91) was observed in association with three or more prescriptions of hydrochlorothiazide at least 2 years before diagnosis. [This observation was one of many comparisons. The study reported limited data on potentially confounding factors, i.e. those not available in medical records, e.g. cigarette smoking history. While hypertension was evaluated in the analysis, it was uncertain whether findings for cancer of the renal pelvis could be attributed to hydrochlorothiazide use or to hypertension, since use of other cardiovascular drugs, e.g. Clonidine, Diltiazem, and Gemfibrozil, were also related to risk of renal cell cancer.]

Also using records from the Kaiser Permanente Medical Care Program, Hiatt *et al.* (1994) conducted a nested case–control study of 257 cases of renal cell carcinoma and one-to-one matched controls. Cases included members enrolled in the programme with documented renal cell carcinoma diagnosed between 1964 and 1989 and who had received a standardized multiphasic health check-up (offered from 1964 to 1988) before diagnosis. Controls who had also undergone the multiphasic health check-up were matched to cases on the age (± 1 year) when they had the check-up, and were required to be enrolled in the Kaiser Permanente Medical Care Program when their case was diagnosed. Data on thiazide use up to 6 months before diagnosis (and a matched date for controls), were abstracted from the medical records. An association was found between thiazide use and renal cell carcinoma among women (OR, 4.0; 95% CI, 1.5–10.8) but not men (OR, 1.2; 95% CI, 0.6–2.1) adjusted for multiple potentially confounding factors, including hypertension (Hiatt *et al.*, 1994). Odds ratios did not increase with estimated number of grams used (based on time since first use, duration, and number of mentions of use in the chart). [Data on potentially confounding or modifying factors were available through the multiphasic check-up.]

A cohort analysis of renal cell carcinoma was conducted in the United States Nurses' Health Study and Health Professionals Follow-up Study (HPFS) of 118 191 women and 48 953 men without a history of cancer (Flaherty *et al.*, 2005). Renal cell carcinomas self-reported (up to 2000 in the Nurses' Health Study, and 1998 in the HPFS) were confirmed by medical record in more than 80% of cases, and the 156 women and 110 men with histologically verified (via biopsy,

nephrectomy or autopsy) renal cell carcinoma were included in the analysis. Thiazide use was based on self-report (beginning in 1980 for the Nurses' Health Study, and 1986 for the HPFS) and was updated every 2–4 years. For women, the age-adjusted relative risk estimate was 1.5 (95% CI, 1.0–2.4), and after adjustment for history of hypertension, and updated body mass index was 1.4 (95% CI, 0.9–2.3); among men, the relative risks were 1.5 (95% CI, 0.9–2.5), and 0.8 (95% CI, 0.5–1.5), respectively. The result was not altered when using updated information on thiazide use. [There was limited information on thiazide use derived from a postal questionnaire. As in other studies, it was not possible to exclude the possibility of confounding by hypertension, since hypertension is a major indication for hydrochlorothiazide use. Hypertension was reported to be an independent risk factor for renal cell carcinoma in this study.]

2.3 Other cancers

Other cancers were assessed in analyses of standardized morbidity ratio using the Kaiser Permanente Medical Care Program prescription pharmacy database and the Kaiser Permanente cancer registry with the northern California (USA) cancer registry as the referent population. Among 143 574 outpatients, with at least one prescription filled between 1969–1973 who were followed for cancer until 1976 using hospital-discharge records for the programme and the cancer registry, Friedman & Ury (1980) found an elevated age- and sex-standardized morbidity ratio for cancer of the prostate (SMR, 1.4; $P < 0.05$). In a subsequent analysis, with follow-up data until 1988, van den Eeden & Friedman (1995) reported a greater than expected incidence of tumours of the gall bladder with thiazide use (16 observed, 8.9 expected; SMR, 1.8; $P < 0.05$). [The limitations of these hypothesis-generating analyses are mentioned in Sections 2.1 and 2.2. Additionally, in the 1995 study, other hypertension drugs also were related to elevated standardized morbidity ratio for cancer of the gall bladder, raising the possibility the association was due to the indication rather the specific drug.]

Two case–control studies of cancer of the breast evaluated self-reported use of thiazides. A case–control analysis of thiazides was conducted in the USA within the Breast Cancer Detection Demonstration Project, a multicentre breast-screening trial involving in-person interviews with women with cancer of the breast (diagnosed between 1973 and 1977) and controls (neither recommended for a biopsy nor had a biopsy during participation in the programme) (Stanford *et al.*, 1986). Response rates were 86% for cases and 74% for controls. Self-reported use of thiazides for at least 6 months compared with women without a history of hypertension was associated with an age-adjusted odds ratio of 1.22 (95% CI, 0.9–1.6). Odds ratios by duration of use were 1.28 for < 5 years, 1.50 for 5–9 years, and 1.33 for ≥ 10 years (P for trend, 0.06). For years since first use were 1.27 for < 5 years, 1.70 for 5–9 years, and 1.06 for ≥ 10 years (P for trend, 0.12).

A more recent population-based case–control study from western Washington State, USA, included 975 cases of cancer of the breast in women aged 65–79 years diagnosed between 1997 and 1999, and identified through the cancer registry for the region (Li *et al.*, 2003). Controls (n = 1007) were identified through Center for Medicare and Medicaid services, and cases were limited to those who were registered in this system. Response rates were 81% of cases and 74% of controls. In-person interviews encompassed a detailed history of cardiovascular medications used, and included duration and dose, using a life-events calendar and photographs of medicines to enhance recall. Ever-use of hydrochlorothiazide was reported by 19% of controls. The odds ratio for cancer of the breast among women who reported use of thiazides for 6 months or more compared with women who

had never used any antihypertension medication was 1.4 (95% CI, 1.1–1.8), and 1.5 (95% CI, 1.1.–2.2) for 6 months to 5 years of use, and 1.3 (95% CI, 1.0–1.7) for > 5 years of use. Multiple potentially confounding factors were taken into consideration, including race, income, marital status, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of oral contraceptive use, ever-use of hormone replacement therapy, first-degree family history of breast carcinoma, smoking status, average daily intake of alcohol, and body mass index. However, none changed the estimate by more than 10%, and thus estimates were only adjusted for age. [This study was large and had relatively extensive information on exposure. The use of recall aids to prompt reporting of drug use was an additional strength. The lack of clear trends with duration could be due to poorer recall for use further in the past, or to lack of a true association.]

A population-based case–control study of invasive epithelial endometrial cancer evaluated thiazide use in New Jersey, USA (Fortuny *et al.*, 2009). Cases were derived from The Estrogen, Diet, Genetics, and Endometrial Cancer (EDGE) study – a population-based case–control study conducted in six counties in northern New Jersey. Cases diagnosed with endometrial cancer between 1 July 2001 and 30 June 2005 were identified by the cancer registries for the region and state. To be eligible, cases were required to be aged 21 years and over and residing in one of the six counties (Bergen, Essex, Hudson, Middlesex, Morris, and Union). Controls, without a history of hysterectomy, were identified through random-digit dialling (age, < 65 years) and Centers for Medicare and Medicaid records. Response rates were 30% for the cases and 39% for the controls. After adjustment for multiple potentially confounding factors, including age, sex, level of education, smoking, body mass index, hypertension, diabetes, and use of other drugs, the overall odds ratio for use of thiazides for at least 6 months was 1.8 (95% CI, 1.1–3.0) [compared with those with no use or use for less than 6 months]. Odds ratios were 1.6 (95% CI, 0.8–3.5), 1.2 (95% CI, 0.6–2.8), 2.4 (95% CI, 1.2–4.8) for < 3, 3–6, and > 6 years of use, respectively (*P* for trend, 0.39). [Low response rates could have introduced selection bias.]

A cohort analysis was conducted of 14 166 individuals recruited between 1990 and 1992 to participate in the Bezafibrate Infarction Prevention study in Israel (Tenenbaum *et al.*, 2001). Participants were followed for incidence and mortality from cancer until 1996 using the Israel population registry and national cancer registry. Participants included those with a history of heart disease (myocardial infarction, stable angina syndrome) but without a permanent pacemaker implantation, cerebrovascular disease, chronic hepatic or renal disease, peripheral vascular disease, malignant disease, estrogen therapy, type 1 diabetes mellitus, or use of lipid-modifying drugs. Incidence of all cancers was increased among those who used hydrochlorothiazide (hazard ratio, HR, 1.41; 95% CI, 0.97–2.05) or a combination hydrochlorothiazide/amiloride therapy (HR, 1.45; 95% CI, 0.88–2.38). An elevated incidence of cancer of the colon was observed among those who used hydrochlorothiazide (n = 5 cases; HR, 2.12; 95% CI, 0.85–5.26) or a combination hydrochlorothiazide/amiloride therapy (n = 4 cases; HR, 3.15; 95% CI, 1.15–8.65). Age, sex, smoking status, and triglycerides were included in the models if they were statistically significant using stepwise Cox models. [No other specific cancer types were mentioned in relation to hydrochlorothiazide. The limitations of this study included the small number of cancers of the colon. There was no information about use, i.e. dose or duration. The precise method of ascertaining medication use was not explained and was assumed to be derived from the intake examination. Given that the cohort was part of a clinical trial, the results may not be generalizable.]

A population-based case–control study was conducted on cancers from 2000 to 2005 using the Danish cancer registry, and drug use was estimated from the Prescription Database of the Danish Medicines Agency (Hallas *et al.*, 2012). A thiazide user was defined as a person having taken 1000 defined daily doses of the drug, and the comparison group was never-users. The odds ratio for all cancers combined was 1.25 (95% CI, 1.22–1.28). [This was a large study with no details on the types of cancer among subjects exposed to thiazides. The association with all cancers combined could be due to confounding by indication as other antihypertension drugs also were related to overall cancer incidence.]

3. Cancer in Experimental Animals

3.1 Oral administration

See Table 3.1

3.1.1 Mouse

In a feeding study, groups of 50 male and 50 female mice (age, 7–8 weeks) were given diets containing hydrochlorothiazide [USP grade] at dietary concentrations of 0 (control), 2500, or 5000 ppm and held until death or completion of the 103–104-week exposure period (NTP, 1989; Bucher *et al.*, 1990). No changes in survival, changes in group mean body weight, or gross clinical evidence of toxicity were identified in male or females exposed to hydrochlorothiazide. A significant increase in the incidences of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined) was seen in males at the highest dose; an increase in the incidence of hepatocellular carcinoma in mice at the highest dose (9 out of 50 versus 4 out of 48) was not statistically significant ($P = 0.161$). Statistically significant, dose-related increases in the incidence of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined) were seen in males. No significant increases in the incidence of any neoplasms were seen in females. [Although significant increases in the incidences of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined) were observed in male mice exposed to hydrochlorothiazide, these findings may have been the result of an unusually low incidence of hepatocellular neoplasms in the dietary control group in this study (15%) compared with those seen in control groups (30%) from the National Toxicology Program (NTP) historical database. The Working Group noted that no data on historical controls were available from the laboratory where this agent was tested.]

3.1.2 Rat

In a feeding study, groups of 24 male and 24 female rats (age, 6–8 weeks) were given diets containing hydrochlorothiazide [USP grade] at a dietary concentration of 0 (control), or 0.1% (1000 ppm) for 104 weeks (Lijinsky & Reuber, 1987). The rats were observed until natural death or moribundity occurred, or the end of the study at 130 weeks. Although the total observation period was not specified, median times of death in male and female rats exposed to hydrochlorothiazide were 111 and 114 weeks, respectively. Median times of death in untreated controls were 107 weeks in males and 122 weeks in females. Dietary administration of hydrochlorothiazide at 1000 ppm was well tolerated. Although body weights were not reported, a high incidence of chronic progressive nephropathy was seen in male and female rats exposed to hydrochlorothiazide; this finding suggested that the dose of 1000 ppm used in the study approached the maximum tolerated dose for this agent. No statistical analyses of the incidences of preneoplastic or neoplastic lesions were reported. The incidence of adrenal pheochromocytoma was increased [$P < 0.005$] from 0 out of 24 in control

Table 3.1 Studies of carcinogenicity in mice and rats given diets containing hydrochlorothiazide

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 103–104 wk NTP (1989), Bucher *et al.* (1990)	Diets containing hydrochlorothiazide at 0 (control), 2500, or 5000 ppm 50 M and 50 F/group (age, 7–8-wk)	Hepatocellular adenoma: 3/48 (6%)*, 8/49 (16%), 14/50 (28%)** (M) Hepatocellular carcinoma: 4/48 (8%), 4/49 (8%), 9/50 (18%) (M) Hepatocellular adenoma or carcinoma (combined): 7/48 (15%)*, 10/49 (20%), 21/50 (42%)** (M)	*$P < 0.01$ (trend) **$P \leq 0.012$	Purity, USP grade No historical control data from the laboratory where this agent was tested Unusually low incidence of hepatocellular neoplasms in the male control group (15%) compared with control groups from the NTP historical database (30%) No significant increases in the incidence of any neoplasm were reported in females
Rat, F344 (M, F) 130 wk Lijinsky & Reuber (1987)	Diets containing hydrochlorothiazide at 0 (control), or 1000 ppm for 104 wk. Rats were held untreated for up to an additional 26 wk 24 M and 24 F/group (age, 6–8 wk)	Adrenal pheochromocytoma: 6/24, 9/24 (M); 0/24, 9/24* (F)	*[$P < 0.005$]	Purity, USP grade No statistical analyses were reported
Rat, F344 (M, F) 105–106 wk NTP (1989), Bucher *et al.* (1990)	Diets containing hydrochlorothiazide at 0 (control), 250, 500, or 2000 ppm 50 M and 50 F/group (age, 7–8-wk)	–	–	Purity, USP grade Decreased body weight in all exposed groups may have reduced sensitivity to neoplastic development No significant increases in the incidence of any neoplasm were reported in either sex

F, female, M, male; USP, United States Pharmacopeia; wk, week

females to 9 out of 24 in exposed females; the incidences of adrenal pheochromocytoma in males were 6 out of 24 and 9 out of 24 in control and treated animals, respectively. [The Working Group noted the unusually high incidence of adrenal pheochromocytoma in males in the control group.] Exposure to hydrochlorothiazide also induced significant increases [$P < 0.001$] in the incidence of parathyroid hyperplasia in males and females.

In a feeding study, groups of 50 male and 50 female rats (age, 7–8 weeks) were given diets containing hydrochlorothiazide [USP grade] at dietary concentrations of 0 (control), 250, 500, or 2000 ppm, and maintained until death or completion of the 105–106-week exposure period (NTP, 1989; Bucher *et al.* 1990). No gross clinical evidence of agent toxicity was identified in either male or female rats exposed to hydrochlorothiazide. Survival curves were very similar in all groups of males. Although an apparent trend towards early mortality was seen in females exposed to hydrochlorothiazide, the differences in survival curves were not statistically significant. Mean body weights in all groups of rats exposed to hydrochlorothiazide were below those in the control groups; at study termination, body weight suppression in both sexes was greater than 15%. This reduction in mean body weight was apparently secondary to suppression of food intake, but was not clearly dose-related. No significant increases in the incidence of any neoplasms were reported in all groups of exposed rats. [The Working Group noted that decreased body weight in all groups exposed to hydrochlorothiazide may have reduced the sensitivity of these animals to neoplastic development.] Confirming the results of Lijinsky & Reuber (1987), significant increases in the incidence of hyperplasia of the parathyroid gland were seen in all groups of exposed rats of males and females.

3.2 Coexposure with modifying agents

In experimental groups that were components of the study described above, Lijinsky & Reuber (1987) exposed groups of 24 male and 24 female F344 rats to diets containing hydrochlorothiazide at 0 ppm (control) or 1000 ppm in combination with sodium nitrite at 2000 ppm for 104 weeks, and maintained until 130 weeks. The study was designed to determine whether exposure to hydrochlorothiazide associated with sodium nitrite could result in the formation of carcinogenic *N*-nitroso compounds in the stomach. No significant increases in neoplastic or preneoplastic lesions were reported. [No statistical analyses of the incidence of preneoplastic or neoplastic lesions were reported.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

(a) Pharmacokinetics of single doses

Pharmacokinetic studies using [^{14}C]hydrochlorothiazide given orally ($n = 4$) or intravenously ($n = 2$) to healthy subjects have shown that hydrochlorothiazide is absorbed mainly (~70%) via the duodenum and upper jejunum, and only to a minor extent via the stomach (Beermann *et al.*, 1976).

High-performance liquid chromatography (HPLC) analysis of plasma and urine samples from 12 healthy volunteers given single oral doses of hydrochlorothiazide (25, 50, 100, or 200 mg as tablets or suspensions) showed that plasma profiles (i.e. mean peak plasma concentrations, times of peak concentrations, areas under

plasma curves) and recovery of unchanged drug in the urine were linearly related to dose (Patel *et al.*, 1984). This was consistent with a previous report from Beermann & Groschinsky-Grind (1977), who used gas-liquid chromatography (GLC) analyses. Absorption from all doses was rapid; peak plasma concentrations were achieved at approximately 2 hours. These findings were common to both tablet and suspension formulations (Patel *et al.*, 1984).

A study in healthy volunteers to evaluate the urinary excretion of hydrochlorothiazide from 25 mg and 50 mg tablets sourced from seven different distributors and at least six manufacturers demonstrated equivalent bioavailability for all products (Meyer *et al.*, 1975). Thus, the bioavailability of hydrochlorothiazide did not appear to differ between different oral preparations (Beermann, 1984).

Absorption of hydrochlorothiazide is generally considered to follow first-order kinetics (Barbhaiya *et al.*, 1982); however, one study of plasma concentrations over the 48 hours following an oral dose of 100 mg in four healthy volunteers (Redalieu *et al.*, 1985) suggested zero-order absorption. [Zero-order kinetics implies accumulation of excess dissolved drug at the absorption site, or saturable absorption, neither of which have so far been demonstrated with hydrochlorothiazide.]

Reports on the influence of ingested food on the absorption of hydrochlorothiazide were conflicting. In a study reporting increased absorption in the presence of food (Beermann & Groschinsky-Grind, 1978b), the mean urinary recovery of an oral dose of 75 mg of hydrochlorothiazide in eight subjects, under both fasting and non-fasting conditions, was found by GLC to be 47% and 55%, respectively. In contrast, a study of eight healthy volunteers each given 50 mg of hydrochlorothiazide reported reduction in plasma absorption (modestly affected by varying accompanying fluid volumes) and reduction in urinary recovery of hydrochlorothiazide taken after (rather than before) food (Barbhaiya *et al.*, 1982). [The inconsistency between these studies was due to procedural differences, for example, differing doses used, and variation in times when food was permitted after dosing. Fasting and non-fasting subjects were permitted food 4 hours after dosing in the later study (Barbhaiya *et al.*, 1982) but not until 10 hours after dosing, in the fasted subjects only, in the earlier study (Beermann & Groschinsky-Grind, 1978b).] It was suggested that prolonged abstinence from food in the fasted group had altered gastrointestinal secretion and motility, affecting drug absorption (Barbhaiya *et al.*, 1982).

Hydrochlorothiazide, in all therapeutic doses, is approximately 40% bound to plasma protein, and accumulates in erythrocytes. The ratio of uptake between erythrocytes and plasma is approximately 3.5 : 1 (Beermann *et al.*, 1976). Equilibrium of hydrochlorothiazide between plasma and erythrocytes is reached 4 hours after an oral dose (Beermann *et al.*, 1976). HPLC analyses in seven healthy volunteers showed that 24 hours after a single oral dose of hydrochlorothiazide of 100 mg, the concentration of hydrochlorothiazide bound to erythrocytes was approximately ninefold the concentration in plasma (Yamazaki *et al.*, 1989).

The study by Beermann *et al.* (1976) of [^{14}C] hydrochlorothiazide given as oral (n = 4) or intravenous (n = 2) doses to healthy subjects demonstrated negligible recovery in the faeces and duodenal bile, and showed that the main excretory route of hydrochlorothiazide was via the kidneys. Mean renal clearance was approximately 300 mL/minute. There was no reabsorption (Beermann *et al.*, 1976). Clearance was by glomerular filtration and active secretion via the organic anion transport system at the proximal tubules (Beermann *et al.*, 1976; Barbhaiya *et al.*, 1982; Kim *et al.*, 2003).

Elimination of hydrochlorothiazide from plasma was biphasic over 24–27 hours; plasma concentrations fell rapidly over the initial 12

hours, and then more slowly (Beermann *et al.*, 1976; Barbhaiya *et al.*, 1982; Patel *et al.*, 1984). The urinary excretion rate closely resembled this time course (Barbhaiya *et al.* 1982). The plasma elimination half-life was about 6 hours initially, but up to 15 hours terminally (Barbhaiya *et al.*, 1982; Patel *et al.*, 1984). Approximately 70% and 90% of the oral and intravenous administered doses, respectively, were recovered unchanged in the urine of healthy volunteers (Beermann *et al.*, 1976), and thus reflected gastrointestinal absorption of hydrochlorothiazide.

(b) Pharmacokinetics of repeated doses

Three patients who had been receiving hydrochlorothiazide only for a minimum of 3 months to treat hypertension (without cardiac failure), were given an oral dose of 50 mg of [^{14}C] hydrochlorothiazide after an overnight fast. Peak concentrations occurred at 3–4 hours in plasma and at 4 to 5 hours in blood cells, and urinary recovery for two of the patients was of the same magnitude as that in healthy subjects, but lower in one patient (who had decreased renal function) (Beermann *et al.*, 1976).

(c) Metabolism

It is generally considered that since hydrochlorothiazide is excreted in urine almost entirely as unchanged drug, it is not metabolized in humans (Beermann *et al.*, 1976). Radiographic analysis of urine extracts (n = 110) collected from five healthy subjects and three patients given [^{14}C]hydrochlorothiazide orally revealed a single spot with the same chromatographic properties as hydrochlorothiazide and representing > 95% of the radiolabel. However, two samples from one subject collected on the second and third days after dosing revealed some radiolabelled material (< 0.5% of total radiolabel excreted) that did not correspond to hydrochlorothiazide (Beermann *et al.*, 1976). The nature of this material was found by Okuda *et al.* (1987) to be 2-amino-4-chloro-1,3-benzenedisulfonamide (ACBS), a hydrolysis product of hydrochlorothiazide. Concentrations of this metabolite were higher (4.3% of hydrochlorothiazide excreted) in patients' urine 24 hours after taking hydrochlorothiazide than in the same batch of bulk tablets (0.4%), so it was unlikely to be a tablet contaminant.

Okuda *et al.*, (1987) also demonstrated that, while concentrations of hydrochlorothiazide in erythrocytes and plasma peaked at 6 hours after dosing and then slowly declined, the concentrations of ACBS were continuing to rise at 24 hours. Thus it seems ACBS is formed by hydrolysis after administration of hydrochlorothiazide, and is excreted more slowly than it is produced. Furthermore, ACBS appears to have a stronger affinity to erythrocytes than does hydrochlorothiazide; concentrations of ACBS and hydrochlorothiazide in erythrocytes were approximately equal, but ACBS concentrations in plasma were approximately 10 times lower than those of hydrochlorothiazide (Okuda *et al.*, 1987).

Metabolites of hydrochlorothiazide were also investigated in urine of six healthy volunteers after oral administration of a single tablet containing 25 mg of hydrochlorothiazide and 25 mg of spironolactone. Hydrochlorothiazide and ACBS (at a concentration at least 10 times higher than the parent drug) and the minor metabolite, chlorothiazide, were detected in the urine by liquid chromatography-mass spectrometry 120 hours after administration (Deventer *et al.*, 2009).

(d) Variation in absorption, distribution, and excretion

(i) Pregnancy

A study of 10 pregnant women given a daily dose of hydrochlorothiazide of 50 mg for at least 2 weeks (to treat oedema and/or hypertension) demonstrated that the diuretic crossed the human placenta, resulting in concentrations in

the umbilical cord plasma that were similar to those in maternal plasma. In amniotic fluid, the concentration of hydrochlorothiazide was higher than that in maternal or umbilical cord plasma by up to 5 and 19 times, respectively (Beermann *et al.*, 1980).

A subsequent case report confirmed these findings, and also reported very low concentrations of hydrochlorothiazide in breast milk (relative to maternal blood). Hydrochlorothiazide was not however detectable (detection limit, 20 ng/mL) in the blood of the nursing infant (Miller *et al.*, 1982).

(ii) Impaired renal function

A study in 23 patients with varying degrees of impaired renal function showed reduction in the extent and rate of elimination of hydrochlorothiazide; only about 10% of an oral dose was recovered, and the elimination half-life was increased from a mean value of 6.4 hours in healthy individuals to 11.5 hours (in patients with a mean creatinine clearance of 60 mL/minute) and to 21 hours (in patients with a mean creatinine clearance of 19 mL/minute). Intestinal absorption was considered not to be reduced in these patients, since the area-under-the-curve values were greater in those with low creatinine clearance than in healthy subjects. In patients with severe renal impairment, the elimination half-life was prolonged further to approximately 34 hours and recovery of hydrochlorothiazide was greatly reduced even after extending the collection period (Niemeyer *et al.*, 1983).

(iii) Gastrointestinal surgery

Absorption of hydrochlorothiazide has been shown to be impaired in patients who have undergone intestinal-shunt surgery for obesity. GLC urine analysis (Backman *et al.*, 1979) for five patients who received an oral dose of hydrochlorothiazide of 775 mg (at times ranging from 1.5 to 6 years after surgery) showed that the recovery of unchanged drug was only 31% of the administered dose (i.e. approximately half the amount normally recovered in the urine).

(iv) Cardiac conditions

The pharmacokinetics of hydrochlorothiazide have been shown to be altered in patients with congestive heart failure (Beermann & Groschinsky-Grind, 1979). GLC analysis of plasma and urine of seven patients given oral hydrochlorothiazide (50–75 mg) indicated substantial reduction in the extent and rate of absorption of hydrochlorothiazide (recovery of only 21–37% of the administered dose in three patients, and delayed plasma peak in another). The total urinary excretion of hydrochlorothiazide in two other patients was approximately 50% of the administered dose. Since the reduced intestinal mobility shown in cardiac failure would be expected to promote the uptake of hydrochlorothiazide, the observed decrease in absorption was suggested to be due to changes in the intestinal wall and/or in blood.

This study also highlighted a substantial reduction in renal clearance (range, 10–187 mL/minute) in these cardiac patients. These patients were older than those studied previously (age, 40–60 years), and it was considered that reduced renal function and age may have been factors in the reduction of absorption (Beermann & Groschinsky-Grind, 1979).

Absorption of hydrochlorothiazide was reported to be unchanged in patients with hypertension (Beermann *et al.*, 1976).

(v) Racial differences

Racial differences in the pharmacokinetics of hydrochlorothiazide have been investigated in a matched group of (nine black and nine white) hypertensive patients given a single dose of 25 mg of hydrochlorothiazide. Analyses of serial samples of blood and urine collected over 36 hours demonstrated that the pharmacokinetics of hydrochlorothiazide did not differ according to race (Ripley *et al.*, 2000).

(vi) Pharmacokinetic and drug interactions

Absorption of an oral dose of 75 mg of hydrochlorothiazide given to six healthy volunteers was shown to be increased by concomitant administration of propantheline. This effect was attributed to the reduction in gastrointestinal motility caused by this anticholinergic drug (Beermann & Groschinsky-Grind, 1978a). The centrally-acting α-adrenergic agonist guanabenz and the excipient polyvinylpyrrolidone 10 000, increased the absorption of hydrochlorothiazide. Cholestyramine and colestipol reduced mean peak plasma concentrations of hydrochlorothiazide (Welling, 1986).

No significant pharmacokinetic interactions have been noted between hydrochlorothiazide and propranolol, metoprolol, sotalol, or acebutolol. A similar lack of significant interactions has been noted between hydrochlorothiazide and spironolactone and indomethacin, allopurinol and its metabolite, oxipurinol, and phenytoin (Welling, 1986).

Early studies on hydrochlorothiazide and triamterene as components of a fixed drug combination revealed differences in bioavailability from combination tablets and capsules, but subsequent work suggested that these differences may have been due to the effects of formulation rather than drug interaction (Welling, 1986).

4.1.2 Experimental systems

A study of intrahepatic distribution in rats demonstrated that, after steady-state intravenous infusion, hydrochlorothiazide distributes homogeneously but not instantaneously throughout the liver. This was proposed to be because hydrochlorothiazide does not undergo metabolism in the liver (AbdelHameed *et al.*, 1993).

In a study in isolated perfused rat kidney, Masereeuw *et al.* (1997) demonstrated that renal clearance of hydrochlorothiazide exceeded clearance by glomerular filtration only at low perfusate concentrations. At higher concentrations (> 100 µg/mL), the renal excretion changed from net secretion to net reabsorption due to saturation of the secretory system and substantial passive tubular reabsorption.

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

See Table 4.1

(a) Mutagenicity

The Working Group did not identify any new data on the mutagenicity of hydrochlorothiazide published since the previous IARC Working Group review (IARC, 1990). In two studies, hydrochlorothiazide was not mutagenic to *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system (Waskell, 1978; Andrews *et al.*, 1984). Hydrochlorothiazide was not mutagenic in bacterial screening systems, with or without enzymatic activation, but can form chemically reactive mutagenic products after reaction with nitrite, a product of nitric oxide (Andrews *et al.*, 1984). [The Working Group noted that only one concentration was used in both studies.] In a third study, 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). Hydrochlorothiazide did not induce reversion in an *arg*⁻ strain of *Escherichia coli* (Hs30R) (Fujita, 1985). At concentrations greater than 500 µg/mL, hydrochlorothiazide produced cytotoxic effects and induced mutations resulting in resistance to trifluorothymidine in L5178Y mouse lymphoma cells in the absence of an exogenous metabolic system (NTP, 1989).

Table 4.1 Genetic and related effects of hydrochlorothiazide

Test system	Results[a]		Concentration or dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
In vitro				
Salmonella typhimurium TA1535, reverse mutation assay	–	–	10 000 µg/plate	Mortelmans *et al.* (1986)
Salmonella typhimurium TA1535, reverse mutation assay	–	–	1000 µg/plate	Andrews *et al.* (1984)
Salmonella typhimurium TA100, reverse mutation assay	–	–	10 000 µg/plate	Mortelmans *et al.* (1986)
Salmonella typhimurium TA100, reverse mutation assay	–	–	5000 µg/plate	Waskell (1978)
Salmonella typhimurium TA100, reverse mutation assay	–	–	1000 µg/plate	Andrews *et al.* (1984)
Salmonella typhimurium TA1537, reverse mutation assay	–	–	10 000 µg/plate	Mortelmans *et al.* (1986)
Salmonella typhimurium TA1538, reverse mutation assay	–	–	1000 µg/plate	Andrews *et al.* (1984)
Salmonella typhimurium TA98, reverse mutation assay	+	–	3333 µg/plate	Mortelmans *et al.* (1986)
Salmonella typhimurium TA98, reverse mutation assay	–	–	5000 µg/plate	Waskell (1978)
Salmonella typhimurium TA98, reverse mutation assay	–	–	1000 µg/plate	Andrews *et al.* (1984)
Escherichia coli (Hs30R) reversion assay in an *arg*⁻ strain	–	NT	0.26 mM	Fujita (1985)
Nondisjunction in *Aspergillus nidulans* spot test	–	NT	NR	Bignami *et al.* (1974)
Chromosome aberration, Chinese hamster ovary cells	–	–	1250 µg/mL	Galloway *et al.* (1987)
Chromosome aberration, Chinese hamster lung cell line	(+)	–	0.5 mg/mL	Ishidate *et al.* (1981)
Sister chromatid exchange, Chinese hamster ovary cells	+	+	900 µg/mL	Galloway *et al.* (1987)
Mutations resulting in trifluorothymidine resistance, L5178Y mouse lymphoma cells	+	NT	500 µg/mL	NTP (1989)
Cytokinesis blocked micronucleus assay, cultured human lymphocytes	+	NT	40 µg/mL	Andrianopoulos *et al.* (2006)
In vivo				
Drosophila melanogaster, sex-linked recessive lethal mutation	–		10 000 ppm in diet	Valencia *et al.* (1985)
Drosophila melanogaster, sex-linked recessive lethal mutation	–		10 000 µg/kg, injection	Valencia *et al.* (1985)

[a] +, positive; (+), weakly positive; –, negative
HID, highest ineffective dose; LED, lowest effective dose; NR, not reported; NT, not tested

In the presence of ultraviolet A irradiation, hydrochlorothiazide significantly enhanced the production of DNA cyclobutane pyrimidine dimers (thymine–thymine dimers, detected by

HPLC) in isolated DNA and in the skin of mice defective in DNA repair (Kunisada *et al.*, 2013).

(b) Chromosomal damage

Chromosomal damage caused by hydrochlorothiazide was reviewed by a previous IARC Working Group (IARC, 1990). In a spot test, hydrochlorothiazide did not induce nondisjunction and mitotic crossing-over in *Aspergillus nidulans* (Bignami *et al.*, 1974). Hydrochlorothiazide did not induce sex-linked recessive lethal mutation in *Drosophila melanogaster* fed or injected with hydrochlorothiazide solutions at 10 mg/mL (Valencia *et al.*, 1985). Significant increases in the frequency of sister chromatid exchange were observed in Chinese hamster ovary cells in the presence and absence of an exogenous metabolic system (Galloway *et al.*, 1987). Although the results of tests for chromosomal aberration were considered to be negative, very high frequencies of chromatid gaps were noted at 900 and 1000 µg/mL (Galloway *et al.*, 1987). Chromosomal aberrations were not found in Chinese hamster lung cells, but polyploidy was observed after treatment with hydrochlorothiazide for 48 hours (Ishidate *et al.*, 1981).

One new study was identified since the previous IARC (1990) evaluation. Hydrochlorothiazide was found to induce micronucleus formation and chromosome breakage in cultured human lymphocytes via chromosome delay (Andrianopoulos *et al.*, 2006).

4.3 Other mechanistic data relevant to carcinogenicity

Effects on cell physiology

Hydrochlorothiazide is a thiazide-based diuretic that acts on an electroneutral Na^+/Cl^- cotransporter in the distal convoluted tubules of kidney nephrons. The major physiological action of hydrochlorothiazide is to compete for the chloride site on this transporter, thus inhibiting Na^+ transport and reducing blood volume. Clinical evidence also indicates that hydrochlorothiazide can act as a photosensitizer in the presence of irradiation by ultraviolet A or ultraviolet B (Addo *et al.*, 1987). The incidence of phototoxic exanthem is "occasional" (> 1/1000 to < 1/100) (Rote Liste Service GmbH, 2012)

4.4 Susceptibility

No data were available to the Working Group.

4.5 Mechanistic considerations

The possible association between exposure to hydrochlorothiazide and cancer of the skin may result from drug-related photosensitization, which would cause DNA damage (production of dimers by hydrochlorothiazide in the presence of sunlight) and may also lead to a chronic inflammatory reaction in the skin.

5. Summary of Data Reported

5.1 Exposure data

Hydrochlorothiazide is a thiazide-based diuretic that is recommended as a first-line therapy for hypertension. Most frequently, hydrochlorothiazide is used with other drugs that lower blood pressure, including in combination products. In the USA, use of hydrochlorothiazide has declined slightly over the past decade.

5.2 Human carcinogenicity data

The occurrence of cancer among patients using hydrochlorothiazide has been examined in cohort and case–control studies from the USA and Denmark, and in an observational cohort within an intervention trial of heart disease patients from Israel. Other cohort and case–control

studies have examined use of thiazides (but not specifically hydrochlorothiazide) in multiple regions of Europe and in the USA.

5.2.1 Cancers of the skin and lip

Associations between use of hydrochlorothiazide and squamous cell carcinoma of the skin or lip were assessed in two case–control studies in Denmark, and California, USA. The case–control study from Denmark reported an excess risk of squamous cell carcinoma of the skin associated with hydrochlorothiazide use, and risk increased with increasing dose; cancer of the lip was not evaluated. A case–control analysis of a cohort study from California detected an excess risk of cancer of the lip and "other skin cancers" (not including squamous cell carcinoma, basal cell carcinoma, or melanoma) among users of hydrochlorothiazide. This was followed by a nested case–control study of cancer of the lip in the same population, which reported a statistically significant twofold increase in risk for three or more prescriptions, and increasing odds ratios with duration of use. This was the only study with adequate statistical power to assess use of hydrochlorothiazide alone. Two other case–control studies of cancer of the skin in Europe and the USA reported increased odds ratios for squamous cell carcinoma of the skin associated with use of thiazide or photosensitizing cardiovascular drugs (mainly thiazides); these findings supported the results of studies reporting on hydrochlorothiazide specifically.

While the available data on hydrochlorothiazide and skin cancer generally suggested associations with squamous cell carcinoma for sites potentially exposed to sunlight (i.e. skin and lip), only a few studies have evaluated the association between hydrochlorothiazide exposure and cancer of the skin and lip, and even fewer studies have examined dose or duration effects. The Working Group considered that the potential confounding effect of sunlight exposure, a major risk factor for squamous cell carcinoma, was minimal, since positive associations were observed in studies that could account for this effect. Effect modification by sun exposure is potentially important, but had not been thoroughly examined.

In contrast to the results for squamous cell carcinoma, results from case–control and cohort studies that examined basal cell carcinoma and malignant melanoma of the skin were weaker, lacked dose–response relationships, or gave results that were close to unity.

5.2.2 Other cancer sites

An increased risk of cancer of the kidney associated with use of hydrochlorothiazide (one study) or thiazide was reported in three studies in two independent study populations in the USA; an earlier study in one of those populations had also found an increased risk of renal cell carcinoma among women with unspecified thiazide use. This association was difficult to interpret owing to potential confounding by hypertension, an independent risk factor for renal disease.

Two case–control studies on cancer of the breast assessed thiazide use: the odds ratios found were 1.2, and 1.4, respectively. Increased risks of cancer of the gall bladder, colon, prostate, and endometrium associated with thiazide use were reported each in a single study.

In conclusion, there were few studies on the risk of other cancers in relation to use of hydrochlorothiazide, and results had the potential to be confounded by drug indication.

5.3 Animal carcinogenicity data

Hydrochlorothiazide was tested for carcinogenicity in one feeding study in male and female mice, in two feeding studies in male and female rats, and in one feeding study with coexposure to sodium nitrite in male and female rats. In the first study, hydrochlorothiazide caused a significant increase in the incidence of hepatocellular

adenoma, and of hepatocellular adenoma or carcinoma (combined) in male mice; there were no significant increases in the incidence of any neoplasm in female mice. In the second study, there was an increased incidence of adrenal pheochromocytoma in female rats. No significant increase in the incidence of any neoplasm was observed in male rats in the second study, or in male and female rats in the third study. The study of coexposure also gave negative results.

5.4 Mechanistic and other relevant data

Hydrochlorothiazide is excreted essentially unchanged in humans.

Hydrochlorothiazide was not mutagenic in standard bacterial screening assays, but produced cytotoxic effects and induced mutation in L5178Y mouse lymphoma cells in the absence of exogenous metabolic activation. Hydrochlorothiazide increased the frequency of sister chromatid exchange, but not chromosomal aberration, in Chinese hamster ovary cells, both in the presence and absence of an exogenous metabolic system. Hydrochlorothiazide induced polyploidy, but not chromosomal aberration, in Chinese hamster lung cells. In-vitro induction of micronucleus formation and chromosome breakage via chromosome delay were observed in human lymphocytes exposed to hydrochlorothiazide.

In the presence of ultraviolet A irradiation, hydrochlorothiazide enhanced the production of DNA cyclobutane–pyrimidine dimers, both in isolated DNA and in the skin of DNA repair-deficient mice.

The possible association between exposure to hydrochlorothiazide and cancer of the skin may result from drug-related photosensitization, which would cause DNA damage (production of dimers by hydrochlorothiazide in the presence of sunlight) and may also lead to a chronic inflammatory reaction in the skin.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of hydrochlorothiazide. Positive associations were observed for squamous cell carcinoma of the skin and lip.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

Hydrochlorothiazide is *possibly carcinogenic to humans (Group 2B).*

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