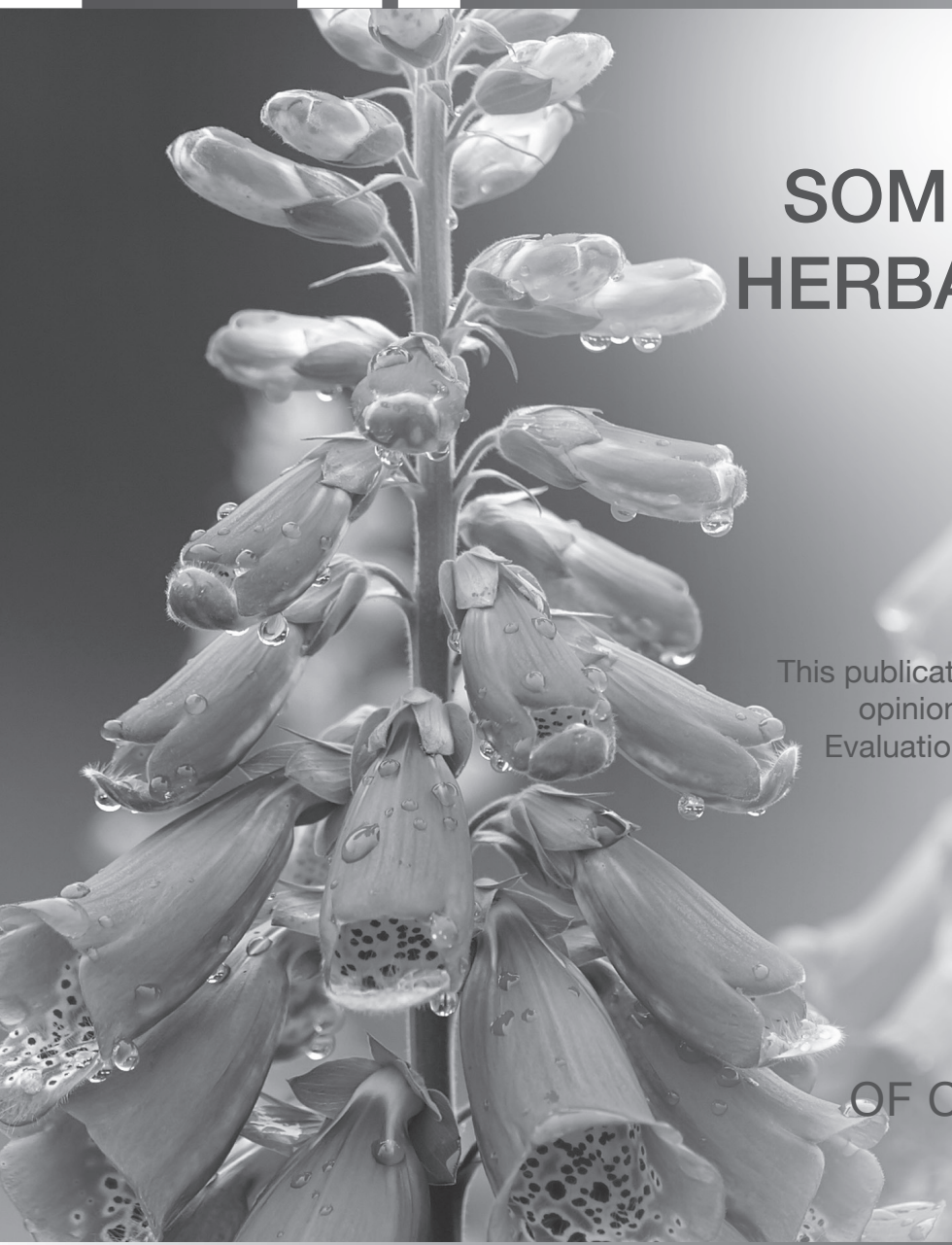
IARC MONOGRAPHS



SOME DRUGS AND HERBAL PRODUCTS

VOLUME 108

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

TRIAMTERENE

1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

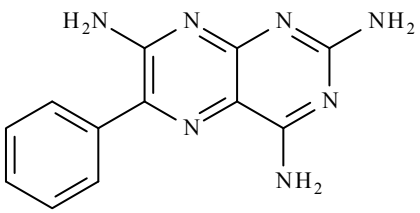
Chem. Abstr. Serv. Reg. No.: 396-01-0

Chem. Abstr. Serv. Name: 2,4,7-Pteridinetriamine, 6-phenyl

IUPAC systematic name: 6-Phenylpteridine-2,4,7-triamine

Synonyms: 6-Phenyl-2,4,7-triaminopteridine; 2,4,7-triamino-6-phenyl-pteridin

1.1.2 Structural and molecular formulae and relative molecular mass



$C_{12}H_{11}N_7$

Relative molecular mass: 253.26 (O'Neil, 2006).

1.1.3 Chemical and physical properties of the pure substance

Description: Odourless yellow powder or crystalline solid, almost tasteless at first and with a slightly bitter aftertaste, acidified solutions give a blue fluorescence (ChemicalBook, 2013)

Melting point: 316 °C

Density: 1.502 g/cm^3 (ChemSpider, 2013)

Solubility: Very slightly soluble in water and in ethanol (96%).

Stability data: Stable in formulation: acid, neutral and alkali. Slowly oxidized upon exposure to air (Bakshi & Singh, 2002; Chemical Book, 2013).

Dissociation constants: pK_a (strongest acidic) = 15.88; pK_a (strongest basic) = 3.11 (DrugBank, 2013)

1.1.4 Technical products and impurities

(a) Trade names

These are some trade names for medications with triamterene as the sole active agent: Ademine; Diren; Ditak; Diucelpin; Diurene; Diuterene; Dyazide; Dyren; Dyrenium; Dytac; Jatropur; Riyazine; Teriam; Triteren; Urinis; Urocaudal (O'Neil, 2006; DrugBank, 2013).

(b) Impurities

The following impurities are listed in the British Pharmacopoeia (2009):

- 5-Nitrosopyrimidine-2,4,6-triamine (nitrosotriaminopyrimidine)
- 2,7-Diamino-6-phenylpteridin-4-ol
- 2,4-Diamino-6-phenylpteridin-7-ol
- Phenylacetonitrile (benzyl cyanide).

1.2 Analysis

Triamterene can be identified by infrared absorption or potentiometric titration assays that use its property of producing an intense blueish fluorescence in a 1/1000 solution of formic acid. The selective estimation of triamterene in the presence of its degradation products or other compounds in biological fluids is mainly carried out by high-performance liquid chromatography (HPLC). Compendial and non-compendial analytical methods are summarized in Table 1.1.

1.3 Production and use

1.3.1 Production process

Triamterene is a synthetic compound that was first synthesized by Spickett & Timmis (1954) by the reaction of 4-amino-5-nitrosopyrimidine with phenylacetonitrile (NTP, 1993).

1.3.2 Use

(a) Indications

Triamterene has been used since 1961 as a potassium-sparing diuretic. It is still chiefly used as an antihypertension agent for the control of elevated blood pressure, as well as for the treatment of interstitial fluid accumulation (oedema), particularly when this co-exists with hypertension. Potassium-sparing diuretics, unlike other classes of diuretics, produce diuresis without loss of appreciable amounts of potassium in the urine. The most commonly reported clinical indications for triamterene in the USA in 2011–2012 are listed in Table 1.2.

Triamterene is recommended as a first-line antihypertensive in the USA (Chobanian *et al.*, 2003), and its use is recommended in combination with another class of antihypertension drug in Europe (Mansia *et al.*, 2007, Mancia *et al.*, 2009). Off-label use for Ménière disease has been reported in the medical literature (van Deelen & Huizing, 1986), and still occurs in the USA (Table 1.2; IMS Health, 2012a).

In the USA, triamterene is approved by the Food and Drug Administration (FDA, 2013) for the management of oedema and as an adjunctive diuretic where its potassium-sparing effect is desired. In 2011–12, 99.5% of its uses were as a combination product with hydrochlorothiazide. The combination of triamterene and hydrochlorothiazide is approved for the treatment of hypertension or oedema in patients who develop hypokalaemia when receiving hydrochlorothiazide alone, or for whom hypokalaemia cannot be risked. Triamterene may also be used alone or as an adjunct to other antihypertension drugs.

The European Union (eMC, 2013) lists three available formulations: triamterene alone, triamterene combined with another diuretic (hydrochlorothiazide, bemetizide, epitizide, trichlormethiazide, xipamide, or furosemide), and triamterene combined with two other antihypertension agents (propranolol/hydrochlorothiazide, reserpine/hydrochlorothiazide, or verapamil/hydrochlorothiazide). These drugs are indicated in the European Union for oedema and hypertension.

Given its use in chronic conditions, triamterene therapy would be expected to be life-long in the absence of adverse effects for the patient.

Triamterene is a weak antagonist of folic acid, and a photosensitizing drug (NTP, 1993; Vargas *et al.*, 1998).

Table 1.1 Some analytical methods for triamterene

Sample matrix	Sample preparation	Assay method	Detection limit	Reference
Compendial methods				
Identity Assay	– –	Infrared spectroscopy Potentiometric titration	– –	British Pharmacopoeia (2009)
Non-compendial methods				
Human serum	Extraction with methyl *tert*-butyl ether, centrifugation, evaporation, reconstitution in mobile phase	HPLC-ECD Column: C_{18} Mobile phase: phosphate buffer : acetonitrile (90 : 10) Flow rate: 0.8 mL/min	5 ng/mL (LOQ)	Richter *et al.* (1996)
Human plasma	Mixing, centrifugation, gentle agitation, evaporated to dryness under N_2, extract was reconstituted with 500 µL of mobile phase	HPLC-UV Column: C_{18} Flow rate: 1 mL/min Detector: fluorescence detector Mobile phase: acetonitrile : distilled water : acetic acid Wavelength: 365 nm	20 ng/mL (LOD)	Yakatan & Cruz (1981)
Human blood, plasma, and urine	Deproteination by adding acetonitrile, mixing, centrifugation	HPLC-UV Column: C_{18} Mobile phase: acetonitrile in 0.02% phosphoric acid solvent system Flow rate: 2 mL/min Excitation wavelength: 365 nm Emission wavelength: 440 nm	20 ng/mL (plasma) 0.5 µg/mL (urine) (LOQ)	Sörgel *et al.* (1984)
Human plasma and urine	Protein precipitation (plasma), centrifugation, collection of supernatant	HPLC Column: C_{18} Fluorescence detector Mobile phase: phosphoric acid and trimethylamine buffer : acetonitrile : methanol (70 : 14 : 8) Flow rate: 0.8 mL/min	1 ng/mL (LOQ)	Swart & Botha (1987)
Human urine	Centrifugation, collection of supernatant	Matrix isopotential fluorometry	2.4 ng/mL (LOD)	Pulgarín *et al.* (2001)
Human urine	Liquid–liquid extraction with ethyl acetate, centrifugation, evaporation, reconstitution in mobile phase	LC-ESI-MS/MS Column: C_{18} Mobile phase: 1% acetic acid and acetonitrile Flow rate: 0.3 mL/min	20 ng/mL	Deventer *et al.* (2002)
Human urine	Filtration through a folded filter	CE-LIF Silica-fused capillary Phosphate buffer Wavelength: 353 nm	50 ng/mL (LOQ)	Horstkötter *et al.* (2002)

Table 1.1 (continued)

Sample matrix	Sample preparation	Assay method	Detection limit	Reference
Human urine	Extraction, preconcentration and derivatization with acetone : methyl iodide (1 : 10)	GC-MS Column: C_{18} Selected ion monitoring	130 µg/L (LOD)	Amendola *et al.* (2003)
Human urine and formulation	Solid-phase extraction	Spectrofluorimetric method Column: C_{18} Mobile phase: phosphoric acid and triethylamine buffer : acetonitrile : methanol (70 : 17 : 3)	0.8 ng/mL (LOD) 2.3 ng/mL (LOQ)	Ibañez *et al.* (2005)
Bovine milk	Extraction with acetonitrile, centrifugation, decantation of supernatant, evaporation to dryness, reconstitution with water	UPLC-ESI-MS/MS Column: C_{18} Flow rate: 0.45 mL/min Multiple reaction monitoring	0.2 µg/kg (LOD) 0.5 µg/kg (LOQ)	Shao *et al.* (2008)
Rat plasma	Tandem solid-phase extraction method by connecting two different cartridges (C_{18} and MCX)	HPLC-UV Mobile phase: acetonitrile : 0.2% acetic acid (20 : 80) Flow rate: 0.8 mL/min Detection wavelength: 265 nm	1.4 ng/mL (LOD) 4.8 ng/mL (LOQ)	Li *et al.* (2011)

CE-LIF, capillary electrophoresis-laser-induced fluorescence; GC-MS, gas chromatography-mass spectrometry; HPLC, high-performance liquid chromatography; HPLC-ECD, high performance liquid chromatography-electrochemical detection; LC-ESI-MS/MS, liquid chromatography-electrospray ionization-tandem mass spectrometry; LOD, limit of detection; LOQ, limit of quantitation; min, minute; NR, not reported; UPLC-ESI-MS/MS, ultra performance liquid chromatography-electrospray ionization- tandem mass spectrometry; UV, ultraviolet

Table 1.2 Most commonly reported clinical indications for triamterene in the USA, 2011–2012

Diagnosis[a]	ICD-9 code	Drug uses (thousands)	Percentage of total
Essential hypertension, NOS	401.90	4824	84.6
Oedema, NOS	782.30	141	2.5
Hypertensive heart disease, other	402.90	136	2.4
Hypertension, benign	401.10	60	1.0
Ménière disease	386.00	56	1.0
Chronic ischaemic disease, unspecified, with hypertension	414.50	44	0.8
Hypertensive renal disease	403.90	43	0.8
Metabolic/insulin resistance syndrome	277.70	29	0.5
Swelling of foot	729.80	24	0.4
Arteriosclerotic heart disease with hypertension	414.20	22	0.4
All other diagnoses	–	323	5.7
Total with reported diagnoses	–	5703	100.0

[a] No diagnosis was stated for 0.5% of drug uses
From IMS Health (2012a)
ICD-9, International Classification of Diseases Ninth Revision; NOS, not otherwise specified

(b) Dosage

In the USA, triamterene alone is available in doses of 50 mg and 100 mg. In combination with hydrochlorothiazide, triamterene doses of 37.5 mg, 50 mg and 75 mg are used. In 2011–12, IMS Health National Disease and Therapeutics Index (NDTI) data showed that the most commonly used form was triamterene 37.5 mg/hydrochlorothiazide 25 mg. Once-per-day dosing predominates (94%). The mean daily dosage among patients taking triamterene is 37 mg per day (IMS Health, 2012a).

In the European Union, triamterene is available as a single agent (50 mg), in combination with hydrochlorothiazide (50 mg with 25 mg hydrochlorothiazide), and in combination with furosemide (50 mg triamterene with 40 mg furosemide) (eMC, 2013).

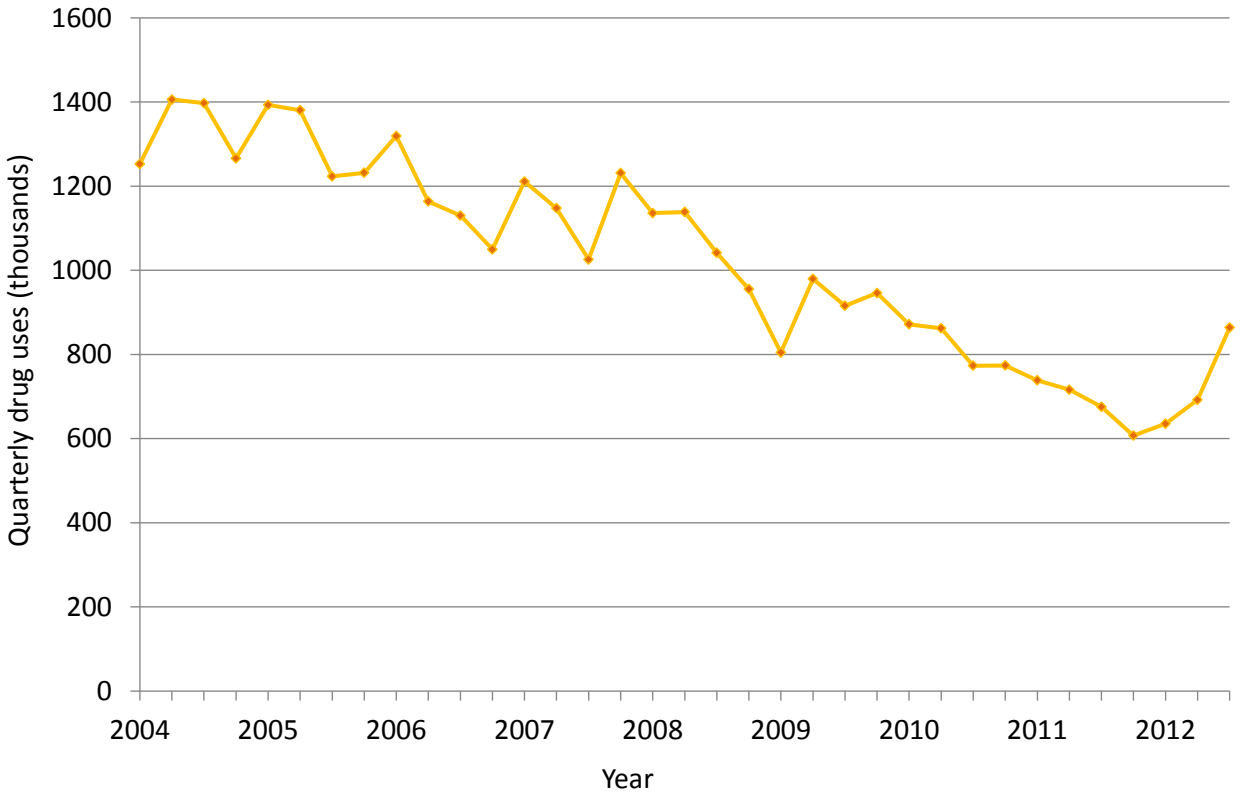
(c) Trends in use

Triamterene is a less commonly used antihypertension agent in the USA, accounting for 3% of the medications prescribed for high blood pressure. Other members of the potassium-sparing diuretic class, spironolactone and amiloride, are chemically distinct from triamterene in several important respects (Wang *et al.*, 2007; Gu *et al.*, 2012).

In the USA, triamterene is used moderately, with 2.8 million drug uses in 2012 according to IMS Health NDTI data (IMS Health, 2012a). Its use has declined by 47% since 2005 (Fig. 1.1). Approximately 1.2 million patients in the USA received triamterene in 2012 (IMS Health, 2012a). According to the IMS Health National Prescription Audit Plus, there was a total of 5.2 million prescriptions containing triamterene dispensed in the USA in 2012, a decrease of 32% from 7.6 million prescriptions in 2008 (IMS Health, 2012b). In 2012, nearly all triamterene (99.6%) was dispensed in the form of combination products containing hydrochlorothiazide (IMS Health, 2012b).

Total worldwide sales of triamterene were US$ 141 million in 2012 according to IMS Health MIDAS data, with 80% occurring in the USA. The only other nation with sales of greater than US$ 5 million was Germany (US$ 11 million) (IMS Health, 2012c).

Fig. 1.1 Use of triamterene reported by office-based physicians, USA



Prepared by the Working Group based on data obtained from IMS Health (2012a)

1.4 Occurrence and exposure

Triamterene does not occur in nature.

Human exposure is predominantly from use as a medication. Occupational exposure in manufacturing is also likely to occur.

1.5 Regulations and guidelines

Triamterene has been widely approved by drug regulatory agencies around the world. In the USA, it was approved by the Food and Drug Administration in 1964 (FDA, 2013). [The Working Group did not identify extraordinary regulatory restrictions on the use of triamterene as a medication, or regulations on environmental exposure.]

2. Cancer in Humans

2.1 Background

Five case–control studies, including two nested case–control studies, assessed the association between triamterene and cancer. Cancer of the breast was investigated in three studies, and cancers of the lip and colon were each assessed in one study; however, only one study on cancer of the breast reported risk estimates specifically for triamterene. The studies are reported below, organized by relevance, and in Table 2.1.

Table 2.1 Case–control studies of cancer and triamterene

Reference Study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Williams *et al.* (1978) USA Period, NR	481 1268	Population	Mailed questionnaires to patients confirmed via physician questionnaire	Breast	Triamterene (ever-use) > 1 yr Recent use ≥ 5 yr	4 NR 0	0.4 $P > 0.05$ 0.4 $P > 0.05$ NR	Age, race, centre. Other risk factors did not have confounding effects Response rate: patient questionnaire, 88%; physician questionnaire, 73%. Triamterene usually used in combination with thiazide. Only four exposed cases treated with triamterene for > 1 yr
Friedman *et al.* (2012) San Francisco, USA, 1994–2008	712 22 904	Nested case–controls; cohort of health-care subscribers	Pharmacy database (prescriptions dispensed)	Lip (squamous cell carcinoma, 97%)	HCTZ/triamterene, prescriptions before cancer diagnosis, ≥ 3 < 1 yr supply 1 to < 5 yr supply ≥ 5 yr supply	71 NR NR NR	1.98 (1.52–2.58) 0.91 (0.60–1.39) 1.87 (1.37–2.57) 2.82 (1.74–4.55)	Smoking White, non-Hispanic without HIV or organ transplant; cases identified by linking to cancer registry; controls randomly selected and matched on age, sex, and year of cohort entry; analysis, 2-yr lag
Mack *et al.* (1975) Los Angeles, USA, 1971–5	99 396	Nested case–controls (retirement community, enrolled from 1968 to 1973)	Medical records; not blinded	Breast	Hypertensive drugs (triamterene alone, 19%) – ever-use. Never used rauwolfia class of drugs Ever-used rauwolfia class of drugs	NR	0.9 [CI cannot be calculated] 2.9 [CI cannot be calculated]	Women, age 53–89 yr; controls matched by age, community entry; cases identified from community records or surrounding hospital and surveillance programmes

Table 2.1 (continued)

Reference Study location and period	Total No. cases Total No. controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Coogan *et al.* (2009) Boston, New York, Philadelphia, Baltimore, USA, 1976–2007	5989 5504	Hospital medical records	Nurse administered questionnaire/ self-reported	Breast	Regular use (4×/wk for at least 3 mo) potassium-sparing diuretics that did not contain thiazide	21	1.22 (0.61–2.46)	Race, education, menopausal status, parity, BMI, female-hormone use, oral contraceptives, and alcohol Women, aged 22–79 yr; controls matched to cases on age, interview year, study centre
					Duration (yr):			
					< 5	10	1.50 (0.57–3.96)	
					≥ 5	11	1.05 (0.38–2.88)	
					P for trend		0.64	
Coogan & Rosenberg (2007) Massachusetts, USA, 2001–4	1229 1165	Population	Telephone interview	Colorectum	Dihydrofolate reductase inhibitors (triamterene, methotrexate, and sulfasalazine)			Age, sex, NSAID use, number of doctor visits, alcohol consumption, education, vitamin use, colonoscopy, dietary factors Age, 50–74 yr. Factors considered but had little effect on odds ratio: race, exercise, BMI, family history, cholecystectomy, smoking status, hormonal replacement therapy. Most common folate antagonist: triamterene (30%)
					Regular use	34	1.6 (0.9–2.8)	
					< 5 yr	16	1.3 (0.6–3.0)	
					≥ 5 yr	18	1.9 (0.8–4.2)	
					P for trend		0.6	

BMI, body mass index; CI, confidence interval; HCTZ, hydrochlorothiazide; mo, month; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; wk, week; yr, year

2.2 Triamterene and cancer of the breast

Odds ratios (OR) specific for triamterene use were reported in a case–control study of 481 women with cancer of the breast, 421 women with benign breast lesions, and 1268 controls identified from a mammography screening project in the USA (Williams *et al.*, 1978). A small proportion of subjects were treated with triamterene, and only four women used it for more than 1 year. Most women also took other drugs. Triamterene use, both ever and recent, was associated with a decreased risk of cancer of the breast. Odds ratios adjusted for age, race, and centre were 0.4 (95% CI, not reported; $P > 0.05$) for both exposure periods. Triamterene use (ever or for 5 years) was associated with a non-significantly increased risk of benign breast lesions; however, triamterene was generally given in combination with thiazide, which was an independent risk factor for benign breast lesions in this study. [The strengths of this study were the verification of exposure information and detailed information on multiple-drug use and potential confounders. However, the study had a limited ability to evaluate the risks specific for triamterene use because only a small number of subjects were treated with triamterene and most were exposed to multiple drugs.]

2.3 Combined use of triamterene and hydrochlorothiazide, and cancer of the lip

Friedman *et al.* (2012) performed case–control analyses of the association between cancer of the lip and use of common antihypertension drugs in a cohort of medical-insurance subscribers in San Francisco, USA. Triamterene combined with hydrochlorothiazide (see *Monograph* on hydrochlorothiazide in this volume) was among the most common prescriptions for diuretics, but triamterene was not assessed separately. Cases of cancer of the lip (squamous cell carcinoma, 97%) were identified via the programme's cancer registry, and drug use was determined from pharmacy database. Analyses were based on 712 cases and 22 904 matched controls and were lagged by 2 years. The smoking-adjusted odds ratio for cancer of the lip and at least three prescriptions for hydrochlorothiazide-triamterene was 1.98 (95% CI, 1.52–2.58); and the risk increased with increasing duration of use. For prescriptions of 1 to < 5 years, the adjusted odds ratio was 1.87 (95% CI, 1.37–2.57), and for prescriptions of ≥ 5 years the adjusted odds ratio was 2.82 (95% CI, 1.74–4.55). Odds ratios for hydrochlorothiazide were higher than those for the hydrochlorothiazide-triamterene combination. [This study was relatively informative for evaluating the effects of treatment with hydrochlorothiazide-triamterene combined and risk of cancer of the lip because of its large size, nested design, use of a pharmacy database for drug usage, and consideration of potential confounders by study-selection criteria and multivariable analysis. While the study did not adjust for exposure to sunlight, it seems unlikely that exposure to sunlight was sufficiently greater in cases than controls to account for the increase in risk by up to threefold. Nevertheless, the study was not informative for evaluating specific effects of triamterene and risk of cancer.]

2.4 The drug class including triamterene, and cancer of the breast or colorectum

Mack *et al.* (1975) evaluated the association of cancer of the breast with antihypertension drugs in a nested case–control study among residents of a retirement community in Los Angeles, USA. The study included 99 cases of cancer of the breast and 396 controls matched for age and entry date, and information about medication was abstracted from medical records of the community health

centre. The rauwolfia class of drugs, including reserpine, were the primary focus of the study, but some analyses were conducted for other antihypertension drugs (methyldopa alone or combined with other drugs, 35%; triamterene alone, 19%; chlorthalidone alone, 15%; hydralazine alone, 15%; spironolactone alone, 7%; guanethidine alone, 3%; and combined drugs not including methyldopa, 6%). The odds ratio for ever-use of other antihypertension drugs was 0.9 (95% CI, not reported) among women who never used the rauwolfia class of drugs, and 2.9 (95% CI, not reported) among ever-users of the rauwolfia class of drugs. [The major limitations of the study were the lack of information specific for triamterene, and the potential for confounding by other antihypertension drugs. Other limitations were the inadequate exposure information, low prevalence of exposure (14% in controls), short follow-up (in part due to the advanced age of the subjects), and the potential lack of generalizability to the general population because of the restricted subject population.]

Another study of cancer of the breast evaluated risks associated with several different classes of diuretics, including thiazides, potassium-sparing diuretics that do not contain thiazide (including triamterene), and loop diuretics, using medical records of several hospitals for 1976–2007 (Coogan *et al.*, 2009). The study included 5989 cases of invasive cancer of the breast, and 5504 matched hospital controls with diagnoses unrelated to use of diuretics. The adjusted odd ratio for cancer of the breast and regular use (defined as four times per week for at least 3 months) of potassium-sparing diuretics was 1.22 (95% CI, 0.61–2.46). The odds ratio was elevated for use for < 5 years (adjusted OR, 1.50; 95% CI, 0.57–3.96), but not for use for ≥ 5 years. [The major limitations of the study were the lack of information specific for triamterene, and the low percentage of the population using potassium-sparing diuretics (21 out of 5504 controls). The potential for recall bias was reduced by the use of hospital controls.]

A case–control study of colorectal cancer grouped triamterene with antagonists of folic acid rather than other antihypertension drugs (Coogan & Rosenberg, 2007). The study included 1229 cases of adenocarcinoma of the colon and rectum identified from cancer registries and participating hospitals in Massachusetts, USA, and 1165 population-based controls matched for age, sex, and geographical location; cases and controls were free from Crohn disease or ulcerative colitis. Triamterene was the most commonly used folic-acid antagonist (30% of all antagonists). Elevated odds ratios were observed for regular use of dihydrofolate-reductase inhibitors, which included methotrexate and sulfasalazine in addition to triamterene (adjusted OR, 1.6; 95% CI, 0.9–2.8) and risks were somewhat higher among those who had used these drugs for 5 years or more (adjusted OR, 1.9; 95% CI, 0.8–4.2). [The study was not specific for triamterene use, and although the population was large, only a small percentage had taken dihydrofolate-reductase inhibitors including triamterene. There was also potential for misclassification of exposure due to self-reporting.]

3. Cancer in Experimental Animals

See Table 3.1

3.1 Mouse

In one study of carcinogenicity with oral administration, referred to hereafter as the first study, groups of 50–60 male and 50–60 female $B6C3F_1$ mice (age, 6 weeks) were given feed containing triamterene (purity, > 99%) at a concentration of 0 (control), 100, 200, or 400 ppm for 2 years. These concentrations were equivalent to average daily doses of approximately 0, 10, 25,

Table 3.1 Studies of carcinogenicity with triamterene in mice and rats

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 104 wk NTP (1993)	*First study:* 0 (control), 100, 200 or 400 ppm in feed: 0, 10, 25, 45 mg/kg bw (M); 0, 15, 30, 60 mg/kg bw (F) *Second study:* 0 (control) or 400 ppm in feed: 0, 40 mg/kg bw (M); 0, 60 mg/kg bw (F) 50–60 M and 50–60 F/group (age, 6 wk), for both studies	*First study* Hepatocellular adenoma: 17/50 (34%), 22/50 (44%), 19/50 (38%), 20/60 (33%) (M); 10/50 (20%)*, 22/50 (44%)**, 23/50 (46%)***, 36/60 (60%)* (F) Hepatocellular carcinoma: 5/50 (10%)**, 7/50 (14%), 3/50 (6%), 13/60 (22%)** (M)[a]; 4/50 (8%), 4/50 (8%), 3/50 (6%), 8/60 (13%) (F) Hepatocellular adenoma or carcinoma (combined): 20/50 (40%), 26/50 (52%), 19/50 (38%), 29/60 (48%)** (M)[b]; 13/50 (26%)*, 26/50 (52%)**, 25/50 (50%)**, 37/60 (62%)* (F)[c] *Second study* Hepatocellular adenoma: 21/50 (42%), 36/50 (72%)* (M); 7/50 (14%), 28/51 (55%)* (F) Hepatocellular carcinoma: 9/50 (18%), 11/50 (22%) (M); 5/50 (10%), 11/51 (22%) (F)[d] Hepatocellular adenoma or carcinoma (combined): 25/50 (50%), 38/50 (76%)** (M)[b]; 10/50 (20%), 31/50 (61%)* (F)[c]	*$P < 0.001$ **$P < 0.05$ ***$P < 0.01$ *$P < 0.001$ **$P < 0.005$	Purity, > 99% Second study performed because of a dosing error in mice at the highest dose in the first study [The Working Group considered that the results for the group at the highest dose could not be evaluated because of overdosing]
Rat, F344/N (M, F) 104 wk NTP (1993)	0 (control), 150, 300, 600 ppm in feed: 0, 5, 10, 25 mg/kg bw (M); 0, 5, 15, 30 mg/kg bw (F) 50 M and 50 F/group (age, 6 wk)	Hepatocellular adenoma: 0/50 (0%), 6/50 (12%)*, 4/50 (8%), 3/49 (6%) (M)[e]	*$P < 0.05$	Purity, > 99% No significant increase in tumour incidence in females

[a] Historical rates of hepatocellular carcinoma in feed studies in control male mice (mean ± SD): 122/865 (14.1% ± 7.2%); range, 3–27%
[b] Historical rates of hepatocellular adenoma or carcinoma (combined) in feed studies in control male mice (mean ± SD): 249/865 (28.8% ± 10.9%); range, 17–58%
[c] Historical rates of hepatocellular adenoma and carcinoma (combined) in feed studies in control female mice (mean ± SD): 98/863 (11.4% ± 7.6%); range, 3–34%
[d] Historical rates of hepatocellular carcinoma in feed studies in control female mice (mean ± SD): 28/863 (3.2% ± 2.9%); range, 0–10%
[e] Historical rates of hepatocellular adenoma in feed studies in control male rats (mean ± SD): 19/799 (2.4% ± 2.9%); range, 0–8%
bw, body weight; F, female; M, male; SD, standard deviation; wk, week

or 45 mg/kg body weight (bw) for males, and 0, 15, 30, or 60 mg/kg bw for females (NTP, 1993). Survival of exposed groups was similar to that of controls except for the group of male mice at 400 ppm. Because of a dosing error, male and female mice at the highest dietary concentration (400 ppm) actually received approximately four times the targeted concentration (approximately 1600 ppm) of triamterene for 7 days at week 40. During week 40, 12 male and 4 female mice died. The surviving mice in the group receiving the highest dose were kept in this study, but because of uncertainty regarding the effect of this 1 week of increased exposure on the outcome of the study, a second study was conducted with groups of 50–60 male and 50–60 female B6C3F$_1$ mice (age, 6 weeks) given feed containing triamterene at 0 (control) or 400 ppm (equivalent to average daily doses of approximately 40 mg/kg bw for males, and 60 mg/kg bw for females) for 2 years.

In the first study, triamterene caused significant increases in the incidences of hepatocellular adenoma in females at the lowest and intermediate doses. [The Working Group considered that the results for the group receiving the highest dose could not be evaluated because of the overdosing.] In the second study, survival of exposed groups was similar to that of controls. There were significant increases in the incidence of hepatocellular adenoma in males and females, and of hepatocellular adenoma or carcinoma (combined) in females. The incidence of liver foci was increased in some groups of treated mice in both the first and second studies. Treatment with triamterene also caused treatment-related thyroid follicular cell hyperplasia.

3.2 Rat

In one study of carcinogenicity with oral administration, groups of 50 male and 50 female F344/N rats (age, 6 weeks) were given feed containing triamterene (purity, > 99%) at a concentration of 0 (control), 150, 300, or 600 ppm. These concentrations were equivalent to average daily doses of approximately 0, 5, 10, or 25 mg/kg bw for males, and 0, 5, 15, or 30 mg/kg bw for females (NTP, 1993). Survival of exposed groups was similar to that of controls. Triamterene caused a significant increase in the incidence of hepatocellular adenoma in male rats at the lowest dose (6 out of 50; 12%), which exceeded the range for historical controls (0–8%;19 out of 799, 2.4%). Hepatocellular adenoma was present in all three dosed groups of males and not in males in the control group. There was no significant increase in the incidence of tumours in female rats. [Hepatocellular adenoma is a tumour that is known to progress to malignancy.]

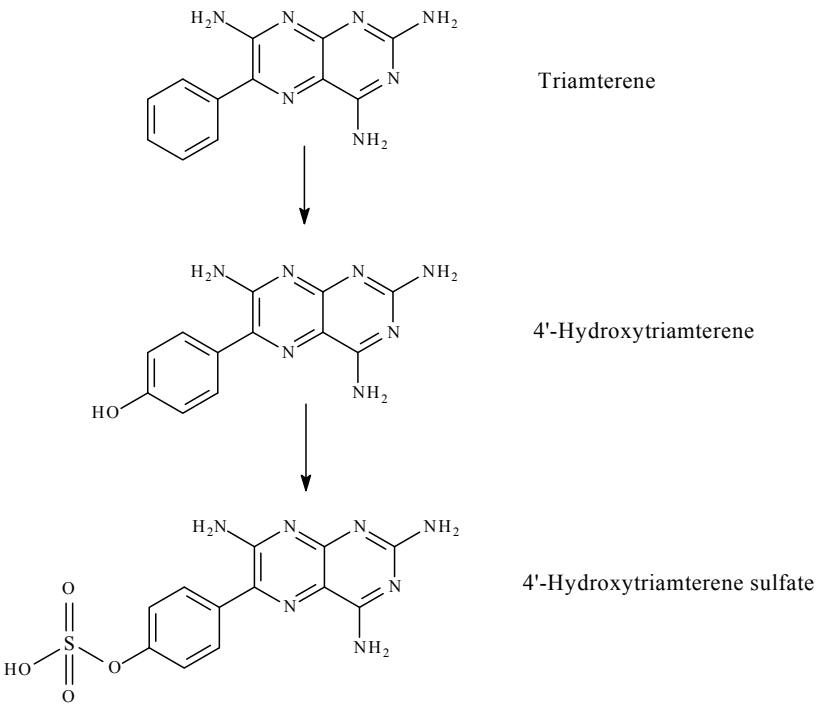
4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

General pharmacokinetic parameters of triamterene and its major metabolite, 4′-hydroxytriamterene sulfate (see Fig. 4.1), were investigated in a randomized crossover trial with six healthy volunteers who were given triamterene by intravenous infusion (10 mg over 10 minutes), or orally (50 mg tablet) (Gilfrich *et al.*, 1983). After intravenous infusion, terminal half-lives for triamterene and 4′-hydroxytriamterene sulfate were 255 ± 42 and 188 ± 70 minutes, respectively. Total triamterene plasma clearance was 4.4 ± 1.41 L/minute, which is indicative of rapid metabolism of this compound. After oral administration, triamterene was rapidly absorbed from the gastrointestinal tract. The parent drug and 4′-hydroxytriamterene sulfate were detectable in plasma after 15 minutes, and maximum concentrations of 26.4 ± 17.7 and 779 ± 310 ng/mL, respectively, were reached after 1.5 hours. The

Fig. 4.1 Chemical structures of triamterene and its metabolites, 4′-hydroxytriamterene and 4′-hydroxytriamterene sulfate



Compiled by the Working Group

half-lives of unchanged triamterene and the metabolite were not significantly different from those observed after intravenous administration.

The bioavailability of triamterene after intravenous or oral administration was calculated from plasma and urine concentrations, and found to be 52 ± 22%, demonstrating considerable inter-subject variability. By inclusion of data for total excretion of triamterene and 4′-hydroxytriamterene sulfate, the absorption was calculated to be 83.2 ± 25.9% (Gilfrich *et al.*, 1983). The high absorption of triamterene is indicative of its ability, as a weak lipid-soluble base (pK_a = 6.2) to cross lipid membranes by non-ionic diffusion (Kau, 1978). Triamterene is more highly concentrated in erythrocytes than in plasma (Gilfrich *et al.*, 1983).

The pharmacokinetic interaction of triamterene and hydrochlorothiazide was investigated in a crossover study of 10 healthy volunteers given oral triamterene (doses, 0, 12.5, 25, 50, or 100 mg), and of 12 healthy volunteers given triamterene (doses, 0, 25, or 50 mg) with hydrochlorothiazide (doses, 12.5, or 25 mg). Coadministration did not affect the renal excretion of either parent drug, but significantly reduced renal excretion of 4′-hydroxytriamterene sulfate (Möhrke *et al.*, 1997).

4′-Hydroxytriamterene sulfate shows more protein binding (91% protein-bound) than triamterene (55%) (Knauf *et al.*, 1983), possibly because of ionic bonding between sulfate and protein, in addition to hydrophobic bonding (Gilfrich *et al.*, 1983). 4′-Hydroxytriamterene sulfate is almost completely eliminated by tubular secretion, while triamterene, although partly eliminated via this route, can also undergo glomerular filtration, due to the fact that a

substantial proportion (45%) is not bound to protein (Knauf *et al.*, 1983).

Triamterene undergoes significant first-pass metabolism with rapid hydroxylation of the phenyl ring at the 4′-position, yielding the phase-I metabolite 4′-hydroxytriamterene (see Fig. 4.1). This intermediate metabolite is transient and is detected at most in trace amounts (< 1 ng/mL) in urine or plasma (Gilfrich *et al.*, 1983). Hydroxylation seems to be mediated virtually exclusively by cytochrome P450 1A2, and inhibition or induction of this isoenzyme will change the time-course of both triamterene and its pharmacologically active phase-II metabolite (Fuhr *et al.*, 2005).

4′-Hydroxytriamterene is rapidly conjugated via cytosolic sulfotransferases to yield the principal phase-II metabolite 4′-hydroxytriamterene sulfate (Gilfrich *et al.*, 1983; NTP, 1993; Horstkötter *et al.*, 2002). In addition, phase-II metabolism produces very small quantities of other metabolites, such as *N*-glucuronides (Lehmann, 1965).

The parent drug and its metabolite 4′-hydroxytriamterene sulfate are excreted in the urine and faeces (Kau & Sastry, 1977; NTP, 1993). Renal clearance of triamterene administered by intravenous infusion (10 mg over 10 minutes) was 0.22 ± 0.1 L/minute, and that of 4′-hydroxytriamterene sulfate was 0.17 ± 0.061 L/minute. Total urinary recovery of triamterene and of the sulfate was 4.5% and approximately 50%, respectively (Gilfrich *et al.*, 1983). Renal clearance of orally administered (50 mg) triamterene and of the sulfate was 0.18 ± 0.05 L/minute and 0.15 ± 0.03 L/minute, respectively (Gilfrich *et al.*, 1983). 4′-Hydroxytriamterene sulfate and *N*-glucuronides were also excreted into the bile (Mutschler *et al.*, 1983; NTP, 1993).

4.1.2 Experimental systems

Intestinal absorption of triamterene in the colon and the whole small intestine of the rat was shown to occur via a carrier-mediated mechanism (Montalar *et al.*, 2003) likely to comprise two carriers, and also via an efflux process (Kau & Sastry, 1977).

The tissue distribution in male Sprague-Dawley rats given [^{14}C]triamterene intravenously showed extensive accumulation of radiolabel (Kau & Sastry, 1977). High concentrations of the parent drug were found in most tissues (except the brain, fat, and testes), and blood concentrations were low. No metabolites were detected. The highest concentrations of triamterene were reached within the first 20 minutes in highly perfused tissues such as kidneys, liver, heart, lungs, and skeletal muscle. The kidneys contained the highest concentrations of triamterene at all timed intervals and doses, but the largest dose deposition was in skeletal muscle (part of the "peripheral compartment"). Elimination was slow (estimated plasma half-life, 2.8 hours), possibly due to triamterene binding to tissue in the "central compartment" (e.g., kidneys, liver). [This study demonstrated the ability of triamterene to bind to tissue, which influences its rate of distribution and elimination.]

Studies of tissue distribution of triamterene in guinea-pigs and baboons reported triamterene concentrations in muscle and heart that were much higher than in plasma, low concentrations in the brain, active transport of triamterene in the kidney, and transfer of triamterene from mother to fetus (Pruitt *et al.*, 1975).

A quantitative study of the renal handling of [^{3}H]triamterene in an isolated, perfused rat-kidney model showed that triamterene undergoes glomerular filtration, active tubular secretion and passive re-absorption by a pH-dependent mechanism (Kau, 1978).

When [^{14}C]triamterene (2 mg/kg bw) was administered subcutaneously to Sprague-Dawley

rats, 45% of the total radiolabel was excreted in the urine, and 50% in the faeces, over 72 hours (Kau *et al.*, 1975). In the urine and faeces, 72–79% of the administered dose was excreted as unchanged triamterene, 10–15% as free 4′-hydroxytriamterene, 1–5% as its sulfate, and 2% as a minor unidentified metabolite. [The low level of sulfate conjugation may have been a consequence of the route of administration.] The liver was identified as the major site of triamterene metabolism; triamterene was not metabolized in the kidney. No metabolites were detected in the plasma.

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

Triamterene (up to 10 000 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA1535, TA1537 or TA100, with or without metabolic activation (S9 from rat or hamster liver) (NTP, 1993). Triamterene did not induce dominant lethal mutations in germ cells of male CD-1 mice when given at doses of up to 100 mg/kg bw per day by gavage for 5 days (Manson *et al.*, 1986).

(b) Chromosomal damage

No increase in the frequency of chromosomal aberration was induced by triamterene at concentrations of up to 600 µg/mL in Chinese hamster ovary cells in vitro in the presence or absence of metabolic activation. Triamterene did induce sister chromatid exchange in Chinese hamster ovary cells in vitro in the presence or absence of metabolic activation (NTP, 1993).

4.3 Other mechanistic data relevant to carcinogenicity

4.3.1 Effects on cell physiology

Triamterene is a potassium-sparing diuretic that blocks the epithelial sodium channel on the luminal side of the collecting tubule in the kidney. Its major physiological action is to inhibit transport of sodium ions and reduce blood volume. The action of triamterene is different from that of thiazide-based drugs, but similar to that of amiloride (Busch *et al.*, 1996). [There is no known link between sodium-channel inhibition and carcinogenesis.]

4.3.2 Effects on cell function

In cultures of the BJAB-B95–8 human lymphoma cell line, there was a dose-dependent inhibition of cell growth, with cell death following extended incubation with triamterene at 80 µM. The activity of dihydrofolate reductase was blocked by triamterene, and its metabolites 4′-hydroxytriamterene and 4′-hydroxytriamterene sulfate are less effective inhibitors of this enzyme (Schalhorn *et al.*, 1981).

Photosensitivity, a known clinical side-effect of triamterene, was demonstrated in vitro in cultures of human peripheral blood lymphocytes and neutrophils co-exposed to triamterene and ultraviolet A (UV-A) irradiation. At a concentration of 60 µg/mL, triamterene decreased cell viability to 40–50%, indicating photosensitization of twofold. Other experiments also showed that triamterene produced singlet oxygen species when irradiated with UV-A light in the presence of molecular oxygen. (Vargas *et al.*, 1998).

Table 4.1 Genetic and related effects of triamterene

Test system	Results[a]		Concentration or dose (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
In vitro				
Salmonella typhimurium TA100, TA98, TA1535, TA1537, reverse mutation	–	–	10 000 µg/plate	NTP (1993)
Chromosomal aberrations, Chinese hamster ovary cells	–	–	600 µg/mL	NTP (1993)
Sister chromatid exchange, Chinese hamster ovary cells	+	+	10 µg/mL, – S9 160 µg/mL, + S9	NTP (1993)
In vivo				
Dominant lethal mutations, germ cells of male CD-1 mice	–	NT	100 mg/kg bw per day for 5 days	Manson *et al.* (1986)

[a] +, positive; –, negative
bw, body weight; HID, highest ineffective dose; LED, lowest effective dose; S9, 9000 × *g* supernatant

4.4 Susceptibility

4.4.1 Liver disease

Patients with liver cirrhosis have reduced ability to hydroxylate triamterene, as evidenced by high plasma concentrations of triamterene and low concentrations of 4′-hydroxytriamterene sulfate. After administration of 200 mg of triamterene, peak plasma concentrations in eight patients without liver disease were 559 ± 48 ng/mL and 2956 ± 320 ng/mL for triamterene and 4′-hydroxytriamterene sulfate, respectively. In the seven patients with alcoholic cirrhosis, peak plasma concentrations of triamterene were increased to 1434 ± 184 ng/mL, while the concentrations of the sulfate were reduced to 469 ± 84 ng/mL. Renal clearance was also reduced in patients with cirrhosis: the clearance of triamterene and the sulfate were 2.8 ± 0.7 and 38.0 ± 6.6 mL/minute, respectively, compared with 14.4 ± 1.5 and 116.7 ± 11.6 mL/minute, respectively, in patients without liver disease (Villeneuve *et al.*, 1984).

4.4.2 Renal impairment

Although renal elimination is only a minor route of excretion for triamterene, it is the main route of elimination of 4′-hydroxytriamterene sulfate. Thus, in individuals with renal impairment, accumulation of the sulfate is substantial and progressive, but negligible for triamterene. The kinetics of triamterene were observed in 32 patients with widely varying degrees of creatinine clearance (10–135 mL/minute), an indicator of renal function. In patients with reduced renal function, significant accumulation in plasma and reduced renal clearance of the sulfate were reported. Plasma concentrations of the parent drug were not increased (Knauf *et al.*, 1983).

4.4.3 Age

Early reports concluded that the mean peak concentration of triamterene after an oral dose of 50 mg is higher in older than in younger patients (84 and 41 ng/mL, respectively), that the time to reach peak concentrations of 4′-hydroxytriamterene sulfate is prolonged [suggesting that hydroxylation decreases with age], and that the systemic clearance of the parent drug and its

metabolite declines significantly with age (NTP, 1993).

In contrast, a more recent study in which an oral dose of triamterene (50 mg) was given to 11 healthy elderly individuals (mean age, 68 ± 5 years), and to 10 healthy young individuals (mean age, 25 ± 2 years) did not report a significant reduction in hydroxylation of triamterene (Fliser *et al.*, 1999). Renal clearance was similar in elderly and young individuals. This study excluded those with conditions that may adversely affect renal or hepatic function (e.g. hypertension, malnutrition, and cardiac failure) and all subjects were on a standardized diet to control intake of protein and electrolytes, particularly sodium. It was assumed by Fliser *et al.* (1999) that the subjects in previous studies may have had various conditions that affected renal and/or hepatic function.

4.5 Mechanistic consideration

Triamterene was not mutagenic in *S. typhimurium*, with or without exogenous metabolic activation, did not induce chromosomal aberrations in Chinese hamster ovary cells, with or without exogenous metabolic activation (NTP, 1993), and did not induce the dominant lethal mutation in the germ cells of male CD-1 mice in vivo (Manson *et al.*, 1986). However, positive results were obtained for induction of sister chromatid exchange in Chinese hamster ovary cells, both with and without metabolic activation (NTP, 1993). Both inhibition of dihydrofolate reductase and photosensitization are possible mechanisms for the induction of DNA damage by triamterene (Schalhorn *et al.*, 1981; Vargas *et al.*, 1998).

5. Summary of Data Reported

5.1 Exposure data

Triamterene is a synthetic potassium-sparing diuretic; unlike other diuretics, it causes limited excretion of potassium in the urine. Triamterene is most often prescribed for hypertension as a combination tablet that includes hydrochlorothiazide. In 2012, while global sales were greatest in the USA (US$ 141 million), the volume of annual prescriptions was modest and had declined over time.

5.2 Human carcinogenicity data

Five case–control studies were available to assess the association between triamterene and cancer.

In two of these studies, all subjects in the treatment group were exposed to triamterene. One of the studies reported a risk estimate that was specific for triamterene and cancer of the breast; however, most of the women took other drugs and few subjects had used triamterene for more than 1 year. The other study reported a relative risk for cancer of the lip and treatment with combined triamterene and hydrochlorothiazide, and thus any effect attributable to triamterene could not be separated from the effects attributable to hydrochlorothiazide.

The three remaining case–control studies reported findings on cancers of the breast or colorectum for triamterene in combination with other drugs (hydrochlorothiazide, other antihypertension drugs, potassium-sparing diuretics, and other inhibitors of dihydrofolate reductase).

The available studies were not informative for evaluation of the association between risk of cancer and exposure specifically to triamterene.

5.3 Animal carcinogenicity data

Triamterene was tested for carcinogenicity by oral administration in two studies in mice and one study in rats.

In a first feeding study in male and female mice, triamterene caused a significant increase in the incidence of hepatocellular adenoma in females. In a second feeding study, triamterene caused significant increases in the incidences of hepatocellular adenoma in males and females, and of hepatocellular adenoma or carcinoma (combined) in females.

In a feeding study in male and female rats, triamterene caused an increase in the incidence of hepatocellular adenoma (a tumour that is known to progress to malignancy) in males. Hepatocellular adenoma was reported in all dose groups, but not in rats in the control group. There was no significant increase in the incidence of tumours in female rats.

5.4 Mechanistic and other relevant data

In humans, triamterene is primarily metabolized to 4′-hydroxytriamterene sulfate via sulfotransferase-mediated conjugation of the phase-I metabolite, 4′-hydroxytriamterene. 4′-Hydroxytriamterene sulfate binds strongly to proteins, to a greater extent than the parent drug. Intravenous administration of radiolabelled triamterene in rats resulted in extensive accumulation of radiolabel, with the highest concentrations in highly perfused tissues, particularly the kidneys.

Triamterene was not mutagenic when tested in *Salmonella typhimurium*, in the presence or absence of exogenous metabolic activation. Triamterene also gave negative results in assays for the induction of chromosomal aberration in Chinese hamster ovary cells, in the presence or absence of exogenous metabolic activation, and did not induce dominant lethal mutation in the germ cells of male CD-1 mice in vivo. Triamterene induced sister chromatid exchange in Chinese hamster ovary cells, in the presence or absence of exogenous metabolic activation. Therefore, triamterene may produce genetic toxicity directly at the chromosomal level without metabolic activation.

Triamterene is an inhibitor of dihydrofolate reductase in vitro; its metabolites 4′-hydroxytriamterene and 4′-hydroxytriamterene sulfate are less effective inhibitors of the enzyme. When irradiated with ultraviolet A light, triamterene produced singlet oxygen species in the presence of molecular oxygen. In-vitro coexposure of human peripheral blood lymphocytes and neutrophils to triamterene and ultraviolet A resulted in decreased cell viability.

Inhibition of dihydrofolate reductase and photosensitization are possible mechanisms for the induction of DNA damage by triamterene.

6. Evaluation

6.1 Cancer in humans

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

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for carcinogenicity of triamterene.

6.3 Overall evaluation

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

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