Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***S.Afr.:*** Bolus Eucalypti Comp; ***Switz.:*** Forapin†.

Apricot

Pharmacopoeias. *Chin.* includes Bitter Apricot Seed, the kernel obtained from various species of *Prunus*. *Jpn* includes a monograph for Apricot Kernel.

Profile

The kernels of the apricot, *Prunus armeniaca* (*Armeniaca vulgaris*; *P. tiliifolia*) (Rosaceae), are used in Chinese medicine for disorders of the respiratory tract and for constipation.

Apricot is a source of persic oil (p.2365). Amygdalin, the major cyanogenic glycoside of apricot kernels, is the major constituent of laetrile (p.2330). Apricot kernels are also a source of pangamic acid (p.2362).

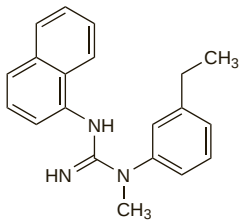
Apricot fruits are used as a food.

Aptiganel *(pINN)*

Aptiganelum. 1-(*m*-Ethylphenyl)-1-methyl-3-(1-naphthyl)guanidine.

Аптиганел

$C_{20}H_{21}N_3$ = 303.4.
CAS — 137159-92-3.



Aptiganel Hydrochloride *(USAN)*

CNS-1102.

$C_{20}H_{21}N_3$,HCl = 339.9.
CAS — 137160-11-3.

Profile

Aptiganel is a guanidine derivative that antagonises the effects of the excitatory amino-acid neurotransmitter glutamate at NMDA-receptors. It has been investigated for the prevention of ischaemic brain damage in patients with traumatic head injury or stroke.

◊ Following dose-ranging studies of aptiganel in healthy subjects[1] and in patients,[2] adverse effects reported[3] in patients with acute ischaemic stroke, at doses that had been neuroprotective in *animals*, included an increase in systolic blood pressure and an excess of CNS effects. A randomised controlled study[4] in patients with acute ischaemic stroke was suspended because of a lack of efficacy and a potential imbalance in mortality compared with placebo.

1. Muir KW, *et al.* Pharmacological effects of the non-competitive NMDA antagonist CNS 1102 in normal volunteers. *Br J Clin Pharmacol* 1994; **38:** 33–8.
2. Block GA, *et al.* Final results from a dose-escalating safety and tolerance study of the non-competitive NMDA antagonist CNS1102 in patients with acute cerebral ischaemia. *Stroke* 1995; **26:** 185.
3. Dyker AG, *et al.* Safety and tolerability study of aptiganel hydrochloride in patients with an acute ischemic stroke. *Stroke* 1999; **30:** 2038–42.
4. Albers GW, *et al.* Aptiganel hydrochloride in acute ischemic stroke: a randomized controlled trial. *JAMA* 2001; **286:** 2673–82.

Arachis Oil

Arachide, huile d', raffinée; Arachidis Oleum; Arachidis oleum raffinatum; Cacahuete, aceite de; Earth-nut Oil; Erdnussöl; Finomított földimogyoróolaj; Ground-nut Oil; Huile d'Arachide; Jordnötolja, raffinerad; Maapähkinäöljy, puhdistettu; Nut Oil; Ol. Arach.; Olej arachidowy oczyszczony; Óleo de Amendoim; Oleum Arachis; Peanut Oil; Podzemnicový olej čištěný; Refined Arachis Oil; Yerfıstığı Yağı; Žemės riešutų aliejus.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *Jpn*. Also in *USNF*.

Eur. also includes hydrogenated arachis oil.

Ph. Eur. 6.2 (Arachis Oil, Refined; Arachis Oil BP 2008). The refined fatty oil obtained from the shelled seeds of *Arachis hypogaea*. A suitable antoxidant may be added. It is a clear, yellowish viscous liquid consisting of glycerides, chiefly of oleic and linoleic acids, with smaller amounts of other acids. It solidifies at about 2°. Very slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

The BP 2008 gives Ground-nut Oil and Peanut Oil as approved synonyms.

Ph. Eur. 6.2 (Arachis Oil, Hydrogenated; Arachidis Oleum Hydrogenatum). Arachis oil that has been refined, bleached, hydrogenated, and deodorised. It is a white or faintly yellowish soft mass that melts to a clear pale yellow liquid when heated. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in petroleum spirit (b.p. 65° to 70°). Protect from light.

USNF 26 (Peanut Oil). The fully-refined (alkali-refined, bleached, and deodorised at 230° to 260°) oil obtained from the seed kernels of one or more of the cultivated varieties of *Arachis hypogaea* (Leguminosae). It is a colourless or pale yellow, oily liquid with a bland taste; it may have a characteristic nutty odour. Very slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, and with ether. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Profile

Emulsions containing arachis oil are used in nutrition. Arachis oil is given as an enema for softening impacted faeces. It is used in drops for softening ear wax (see under Docusates, p.1725) and in emollient creams. Arachis oil is given by mouth, usually with sorbitol, as a gallbladder evacuant prior to cholecystography.

Precautions. It has been suggested that the use during infancy of preparations containing arachis oil, including infant formulae and topical preparations, may be responsible for sensitisation to peanut, with a subsequent risk of hypersensitivity reactions.[1-3] The arachis oil used in such preparations is refined oil and it has been pointed out that such oil should not contain the proteins that produce allergic reactions in susceptible people.[4,5] In the USA, heating of arachis oil during preparation, to further reduce protein content, has been proposed.[6] Nonetheless, some consider that sufficient protein may be present in refined oil to cause sensitisation.[7] However, others have pointed out that to date, there are no reliable data about doses of topical arachis oil needed to induce sensitisation via the epidermal route and that the benefit of protecting skin barrier functions in atopic patients with products using refined arachis oil outweigh possible risks of sensitisation.[8] In the UK, the CSM considered that there was not enough evidence to conclude that medicinal products containing arachis oil could lead to sensitisation.[9] However, although they considered the risk of a reaction to be low, they recommended that patients known to be allergic to peanuts should not use medicines containing arachis oil (nor, because of the possibility of cross-sensitivity, should patients allergic to soya), and that such medicines should include an appropriate warning in the labelling.

1. de Montis G, *et al.* Sensitisation to peanut and vitamin D oily preparations. *Lancet* 1993; **341:** 1411.
2. Lever LR. Peanut and nut allergy: creams and ointments containing peanut oil may lead to sensitisation. *BMJ* 1996; **313:** 299.
3. Lack G, *et al.* Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; **348:** 977–85.
4. Hourihane J O'B, *et al.* Randomised, double blind, crossover challenge study of allergenicity of peanut oil in subjects allergic to peanuts. *BMJ* 1997; **314:** 1084–8.
5. Committee on Toxicity of chemicals in Food, Consumer Products and the Environment. *Peanut allergy.* London: Department of Health, 1998.
6. Wilkin JK, *et al.* Peanut allergy. *N Engl J Med* 2003; **349:** 302.
7. Lack G, *et al.* Peanut allergy. *N Engl J Med* 2003; **349:** 302–3.
8. Ring J, Möhrenschlager M. Allergy to peanut oil — clinically relevant? *J Eur Acad Dermatol Venereol* 2007; **21:** 452–5.
9. Committee on Safety of Medicines/Medicines and Healthcare Regulatory Agency. Medicines containing peanut (arachis) oil. *Current Problems* 2003; **29:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Preparations

BP 2008: Arachis Oil Enema.

Proprietary Preparations (details are given in Part 3)
Austral.: Calogen; ***Chile:*** Oilatum; ***Denm.:*** Olie; ***Fin.:*** Calogen; ***Ger.:*** Olbad Cordes F; ***Indon.:*** Oilatum Cream; ***Irl.:*** Calogen; Fletcher's Arachis Oil; Oilatum Cream; ***Ital.:*** Calogen; ***Mex.:*** Dermo Bell; Nutrisil; Oilatum; ***NZ:*** Calogen; ***S.Afr.:*** Oilatum Cream; ***Singapore:*** Oilatum Cream; ***UK:*** Calogen; Fletchers Arachis Oil Retention Enema†.

Multi-ingredient: ***Austral.:*** Cerumol; Gold Cross Skin Basics Zinc Cream†; Medevac†; ***Austria:*** Balneum F; ***Chile:*** Tarytar†; ***Cz.:*** Balneum Hermal F; ***Ger.:*** Balneum F; Parfenac Basisbad†; ***Irl.:*** Cerumol; Hydromol†; ***Israel:*** Balneum F; Cerumol; ***Ital.:*** Balneum Hermal Forte; ***NZ:*** Medevac†; ***Pol.:*** Balneum Hermal F; ***S.Afr.:*** Cerumol; Haarlemensis; ***Singapore:*** Cerumol; ***Spain:*** Emolytar; ***Switz.:*** Balmed Hermal F; Balneum Hermal F†; ***UK:*** Cerumol; Earex; Hewletts; Nowax; Red Oil; Soothol.

Areca

Areca Nuts; Arecae Semen; Arekasame; Betel; Betel Nuts; Noix d'Arec.

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of areca:
Daka; Gua; Maag; Mak; Marg; Pan parag; Pinang; Pugua; Puwak; Supai; Suparim.

Pharmacopoeias. In *Chin.* and *Jpn*.

Profile

Areca consists of the dried ripe seeds of *Areca catechu* (Palmae) containing the alkaloid arecoline.

Areca is used in Asian countries as a masticatory. It has sialogogue properties and is chewed for its mild intoxicant and euphoriant effects. The usual custom is to chew pieces of areca seed (areca nut; betel nut) wrapped with lime (calcium hydroxide) in the leaf of the betel pepper (betelvine) (*Piper betle*, which is unrelated to areca). This preparation is known as 'betel quid' (betel) or 'paan' (pan-masala), and produces a red juice when chewed, which stains the saliva, teeth and mucosa. Other ingredients that might be added include catechu gum, spices, or tobacco.

Arecoline and arecaidine (produced by the hydrolysis of arecoline when chewed with lime) have cholinergic activity, and adverse effects that may occur with initial or heavy use of areca include excessive salivation, sweating, lachrymation, urinary incontinence, or diarrhoea. An increased incidence of oral submucosal fibrosis, oral leucoplakia, and oral squamous cell carcinoma has been reported following habitual use.

Areca was formerly used in the treatment of tapeworm infection, and arecoline has been used in veterinary medicine as a purgative and taenifuge.

◊ Discussions of the health risks associated with the chewing of preparations containing areca nut by indigenous populations in Asia[1-3] and immigrant groups in the UK,[4] USA,[5] and New Zealand,[6] including acute effects.[2,3,5] See also Adverse Effects of Tobacco Products under Nicotine (p.2352) for reference to mixtures of areca and tobacco.

1. Mack TM. The new pan-Asian paan problem. *Lancet* 2001; **357:** 1638–9.
2. Deng JF, *et al.* Acute toxicities of betel nut: rare but probably overlooked events. *J Toxicol Clin Toxicol* 2001; **39:** 355–60.
3. Chu NS. Effects of Betel chewing on the central and autonomic nervous systems. *J Biomed Sci* 2001; **8:** 229–36.
4. Warnakulasuriya S, *et al.* Areca nut use: an independent risk factor for oral cancer. *BMJ* 2002; **324:** 799–800.
5. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.
6. Yoganathan P. Betel chewing creeps into the New World. *N Z Dent J* 2002; **98:** 40–5.

Carcinogenicity. Precancerous and cancerous conditions of the oral cavity have been attributed to the chewing of preparations containing areca (see above). In betel-chewer's mucosa, the oral mucosa is discoloured and there is desquamation or peeling of the oral epithelium from the traumatic effect of chewing and possibly a chemical action of the constituents. This condition may be a precursor of oral submucosal fibrosis, which is considered to be precancerous.[1] Oral leucoplakia is another precancerous condition that is reported. The role of areca in the development of these conditions and oral squamous cell carcinoma has been debated. The effects may be due to the arecaidine content of areca, the alkalinity of the lime, presence of tobacco, or a combination of these.[2,3] Results from a case-controlled study[4] point to an independent association between oral squamous cell carcinoma and chewing areca seeds in preparations without tobacco compared with non-users of areca. A review[5] of available evidence strongly supports this association.

1. Reichart PA, Philipsen HP. Betel chewer's mucosa—a review. *J Oral Pathol Med* 1998; **27:** 239–42.
2. Norton SA. Betel: consumption and consequences. *J Am Acad Dermatol* 1998; **38:** 81–8.
3. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.
4. Merchant A, *et al.* Paan without tobacco: an independent risk factor for oral cancer. *Int J Cancer* 2000; **86:** 128–31.
5. Nair U, *et al.* Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. *Mutagenesis* 2004; **19:** 251–62.

Effects on the lungs. Evidence suggesting that there is an association between betel-nut chewing and bronchoconstriction in asthmatic patients.[1,2]

1. Taylor RFH, *et al.* Betel-nut chewing and asthma. *Lancet* 1992; **339:** 1134–6.
2. Kiyingi KS. Betel nut chewing and asthma. *Lancet* 1992; **340:** 59–60.

Effects on the nervous system. Areca-nut (betel-nut) chewing is associated with habituation, addiction, and dependence,[1] and CNS symptoms of withdrawal have been described in 2 patients.[2] A case of neonatal withdrawal syndrome in an infant born to a chronic areca-nut user has also been reported.[3] Psychosis has also been reported.[1]

It has been suggested that the muscarinic action of areca alkaloids may have a beneficial effect on symptoms of schizophrenia, and a study of such patients in a Micronesian population provides some support for this idea.[4] However, severe extrapyramidal symptoms followed betel-nut chewing in 2 patients with chronic schizophrenia who were also receiving antipsychotic therapy.[5]

1. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; **34:** 238–43.

2. Wiesner DM. Betel-nut withdrawal. *Med J Aust* 1987; **146:** 453.
3. López-Vilchez MA, *et al.* Areca-nut abuse and neonatal withdrawal syndrome. Abstract: *Pediatrics* 2006; **117:** 203. Full version: http://pediatrics.aappublications.org/cgi/content/full/117/1/e129 (accessed 10/04/08)
4. Sullivan RJ, *et al.* Effects of chewing betel nut (Areca catechu) on the symptoms of people with schizophrenia in Palau, Micronesia. *Br J Psychiatry* 2000; **177:** 174–8.
5. Deahl MP. Psychostimulant properties of betel nuts. *BMJ* 1987; **294:** 841.

Aristolochia

Serpentaria.

NOTE. *Aristolochia clematitis* has also been known as asarabacca (p.2261).

Pharmacopoeias. *Chin.* allows various species of *Aristolochia*.

Profile

Aristolochia spp. (birthworts) including *A. clematitis* and *A. ringens (A. brasiliensis)* have been used in herbal medicine.

Serpentary (serpentaria) is the dried rhizome and roots of *Aristolochia serpentaria* (Virginian snakeroot) and of *A. reticulata* (Texan snakeroot) (Aristolochiaceae). Snakeroot is also used as a common name to describe poisonous *Eupatorium* spp. Preparations of serpentary have been used as bitters. The active ingredient is aristolochic acid, which has been tried in a number of inflammatory disorders, mainly in folk medicine; the sodium salt of aristolochic acid has also been used. However, there is concern over such use since aristolochic acid has been reported to be carcinogenic and nephrotoxic.

Chinese medicine has employed various species of *Aristolochia* including *A. contorta*, *A. debilis* (but see under Adverse Effects, below), and *A. manshuriensis*. The terms Mu Tong and Fangji have been used for *Aristolochia* spp. in traditional medicine.

Adverse effects. Progressive interstitial fibrosis of the kidney related to a slimming regimen containing Chinese herbs had been reported in 70 patients in Belgium by 1993; 30 of these patients had terminal renal failure.[1] Renal failure has also been reported[2] in 2 patients in the UK after ingestion of Chinese herbal medicines that were later found to contain aristolochic acid, a known nephrotoxin;[3] one of these patients subsequently developed invasive urothelial carcinoma.[4] Inadvertent ingestion of aristolochic acid can originate as a result of the substitution of *Aristolochia* spp. (probably *A. manshuriensis*) for other innocuous herbal substances;[2,5] the Belgian cases were probably as a result of substitution of *A. fangchi* extracts for *Stephania tetrandra*.[1] As a result of these cases, the UK MCA issued a permanent ban on *Aristolochia* preparations in 1999. Similar bans have been made in several other countries;[3] in 2004, the Chinese regulatory authority also banned the use of *A. fangchi* and *A. debilis* in traditional medicine formulations. Examination of 39 patients in Belgium with nephropathy associated with *A. fangchi* ingestion had revealed 18 cases of urothelial carcinoma and evidence of mild to moderate dysplasia in 19 patients.[6] There had appeared to be a higher risk of carcinoma with total doses of *A. fangchi* in excess of 200 g.

Aristolochic acid has been proposed as the cause of endemic (Balkan) nephropathy,[7] which is confined to a very specific rural geographical distribution and first described in the 1950s. Data supporting this hypothesis included findings of DNA damage linked to aristolochic acid in kidney samples from affected patients, as well as renal failure in horses who had grazed in the local fields. *Aristolochia clematitis* is endemic to the region and has been found in fields cultivated for wheat grain. It is possible that the local population could be exposed to toxic amounts of aristolochic acid over time from bread made with grain contaminated with *A. clematitis* seeds.

1. Vanhaelen M, *et al.* Identification of aristolochic acid in Chinese herbs. *Lancet* 1994; **343:** 174.
2. Lord GM, *et al.* Nephropathy caused by Chinese herbs in the UK. *Lancet* 1999; **354:** 481–2.
3. Cosyns JP. Aristolochic acid and 'Chinese herbs nephropathy': a review of the evidence to date. *Drug Safety* 2003; **26:** 33–48.
4. Lord GM, *et al.* Urothelial malignant disease and Chinese herbal nephropathy. *Lancet* 2001; **358:** 1515–6.
5. But PP, Ma S-c. Chinese-herb nephropathy. *Lancet* 1999; **354:** 1731–2.
6. Nortier JL, *et al.* Urothelial carcinoma associated with the use of a chinese herb (Aristolochia fangchi). *N Engl J Med* 2000; **342:** 1686–92.
7. Grollman AP, *et al.* Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci U S A* 2007; **104:** 12129–34.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Euserpina Cellulite.

Multi-ingredient: ***S.Afr.:*** Borstol Cough Remedy.

Arnica

Árnica; Arnica, fleur d' (arnica flower); Arnicae Anthodium; Arnicae flos (arnica flower); Arnikablomma (arnica flower); Arnikinkukka (arnica flower); Arnikový květ (arnica flower); Arnikų žiedai (arnica flower); Hegyi árnika virág (arnica flower); Koszyczek arniki (arnica flower); Leopard's Bane; Mountain Tobacco; Wolf's Bane; Wolfsbane.

NOTE. Wolfsbane is also used as a common name for aconite (p.2246).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Arnica Flower; Arnica Flos). It consists of the whole or partially broken, dried flowerheads of *Arnica montana*. It contains not less than 0.4% w/w of total sesquiterpene lactones expressed as dihydrohelenalin tiglate, calculated with reference to the dried drug. It has an aromatic odour. Protect from light.

Profile

Arnica is generally used in the form of the flowerheads of *Arnica montana* (Compositae).

Arnica flower is irritant to mucous membranes and when ingested has produced severe symptoms including gastrointestinal and nervous system disturbances, both tachycardia and bradycardia, and collapse. Tincture of arnica may cause dermatitis when applied to the skin of sensitive persons.

Preparations of arnica flower and arnica root are used as astringents for topical application to unbroken skin in conditions such as sprains and bruises; such preparations are not considered suitable for internal use. Arnica flowers are the source of arnica oil, which has been used similarly.

Herbal preparations containing arnica are available for oral use.

Homoeopathy. Arnica has been used in homoeopathic medicines under the following names: Arnica montana; Arnica, Flos; Arnica montana e flore; Arnica montana ex herba; Arnica, Planta tota; Arnica montana ex planta tota; Arn. mont. Some homoeopathic preparations are available for oral use.

◊ References.

1. Leivers K. Unravelling the confusion around arnica's herbal and homoeopathic use. *Pharm J* 2005; **275:** 289–91.
2. Kouzi SA, Nuzum DS. Arnica for bruising and swelling. *Am J Health-Syst Pharm* 2007; **64:** 2434–43.

Preparations

Ph. Eur.: Arnica Tincture.

Proprietary Preparations (details are given in Part 3)

Arg.: Herbaccion Desinflamante†; ***Austral.:*** Sports Ice Bruising Relief; ***Belg.:*** Arnican; ***Chile:*** Arnikaderm; ***Fr.:*** Arnican; Pharmadose teinture d'arnica; ***Ger.:*** Arnikatinktur; Arthrosenex AR; Doc; Enelbin-Salbe; Hyzum N†; Vasotonin†; ***Mex.:*** Balsamo Nordin; Estimul; ***Port.:*** Arnigel; ***Singapore:*** SinEccH; ***UK:*** Arnicare; Atrogel.

Multi-ingredient: ***Arg.:*** Fluido; ***Austral.:*** Joint & Muscle Cream; Percutane; ***Austria:*** Arnicet; Asthmatee EF-EM-ES; Berggeist; Cional; Dynexan; Heparin Comp; Rheuma; Sportino Akut†; ***Belg.:*** Älgi-Cool; Purigel Crisp; Purigel NF; ***Braz.:*** Dermol†; Traumed†; ***Chile:*** Lefkaflam; Matikomp; ***Cz.:*** Arnidol; Heparin-Gel†; ***Fr.:*** Arnicadol; Creme Rap; Decramp; Dermocica; Evarose; Lelong Contusions†; ***Ger.:*** Arnikamill†; Cefawell†; Combudoron; Dolo-cyl; Essaven Sport†; Gothaplast Rheumamed AC; Heparin Comp†; Heparin Kombi-Gel†; Heusin†; Lindofluid N; Retterspitz Ausserlich; Retterspitz Quick; Rhoival†; Sportino Akut; Stullmaton†; Trauma-cyl; Varicylum-S; Venengel†; Vitosal†; ***Hong Kong:*** New Patecs A; ***Ital.:*** Flebolider; Flodolor; Venalta; ***Malaysia:*** Arnica Comp†; ***Mex.:*** Reudol; ***Pol.:*** Arcalen; Arnisol; Dentosept; Dentosept A; Emorect; Escalar; Prostapol; Reumobonisol; Stomatosol; Uroprost; Venoforton; ***S.Afr.:*** Arnica Massage Oil; Combudoron; Dynexan; Lotio Pruni Comp cum Cupro; Muscle Rub; Wecesin; ***Spain:*** Arnicon†; Encialina†; ***Switz.:*** Combudoron; Eubucal†; Euceta avec camomille et arnica; Fortacet; GU Eau†; Onguent aux herbes Keller; Perskindol Cool Arnica; Topaceta; Wecesin†; ***UK:*** Hansaplast Herbal Heat Plaster; Profelan; ***Venez.:*** Andantol Jalea; Biomicovo†; Gelsem.

Arsenic Trioxide *(USAN)*

Acidum Arsenicosum Anhydricum; Arseni Trioxydum; Arsenic; Arsenic Oxide; Arsénico, trióxido de; Arsenicum Album; Arsénieux, anhydride; Arsenii trioxidum; Arsenious Acid; Arsenous Oxide; White Arsenic. Diarsenic trioxide.

As_2O_3 = 197.8.

CAS — 1327-53-3 (arsenic trioxide); 7784-45-4 (arsenic triiodide).

ATC — L01XX27.

ATC Vet — QL01XX27.

Pharmacopoeias. In *Jpn.*

Eur. (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Arsenious Trioxide for Homoeopathic Preparations; Arsenii Trioxidum ad Praeparationes Homoeopathicae). A white or almost white powder. Practically insoluble to sparingly soluble in water; it dissolves in solutions of alkali hydroxides and carbonates.

Adverse Effects

The toxicity of arsenic compounds varies according to chemical composition, solubility, and valency. Inorganic arsenic compounds are much more toxic than organic compounds and elemental arsenic is the least toxic. Toxicity increases with increasing solubility, and trivalent (arsenite) compounds are more toxic than pentavalent (arsenate) compounds. Arsenic exerts its effects through a variety of pathophysiological mechanisms such as induction of oxidative stress and binding to sulphydryl groups in enzymes, and it has the potential to affect most of the major organ systems in the body; it also induces alteration in gene expression.

Acute poisoning. Estimates of lethal and toxic oral doses vary: the lethal dose of arsenic trioxide has been reported to be around 100 to 300 mg; a dose of 1 mg/kg of arsenic may be lethal in children; acute toxic doses of arsenic compounds have been reported to range from 1 mg to 10 g. Symptoms of acute poisoning occur within 30 minutes to several hours after ingestion and food delays the onset.

Early features of acute arsenic poisoning following ingestion involve the gastrointestinal tract with common symptoms of a metallic or garlic taste, a burning sensation in the mouth, dysphagia, abdominal pain, severe nausea, projectile vomiting, haemorrhagic gastritis, and profuse 'rice-water' diarrhoea leading to hypovolaemic shock; the breath may have an odour of garlic. In the absence of adequate treatment, death can occur within 24 hours of a severely toxic dose. Absorption of arsenic may produce multisystem toxicity days or weeks later, which could include cardiomyopathy, anaemia, leucopenia, skin disorders, acute respiratory distress syndrome, hepatitis, renal failure, encephalopathy, and peripheral polyneuropathy.

Arsenic compounds are irritant and corrosive when inhaled or in contact with the skin or eyes; acute systemic effects may occur after inhalation or skin contact.

Chronic poisoning. Arsenic is widely distributed in the environment: the smelting industry (non-ferrous metals) is a major industrial source of arsenic contamination in the soil, water, and air; mining residues and arsenical pesticides and wood preservatives also contribute to soil and water contamination. Seafood is a source of organic arsenic. Occupational exposure is a potential cause of chronic arsenic toxicity but in the general population, food and drinking water is usually the source of arsenic.

Chronic arsenic poisoning or occupational exposure typically produces varied skin disorders appearing over 1 to 10 years, particularly hyperkeratosis, especially affecting the palms and soles, and changes in skin pigmentation. Transverse white lines (Mee's lines) may appear in the nails several weeks after absorption. Gastrointestinal disturbances may occur, although are less likely with chronic exposure. Hypertension, cardiovascular disorders, and diabetes mellitus have been associated with chronic arsenic poisoning. Jaundice may occur as a result of hepatomegaly and portal hypertension may eventually develop. Encephalopathy and peripheral neuropathies may also occur. Arsenic is toxic to the bone marrow and produces a wide range of blood disorders including leucopenia and aplastic anaemia. Chronic exposure to arsenic has been associated with neoplasms of the skin, lungs, bladder, liver, and kidney. Chronic inhalation of arsenic salts may result in perforation of the nasal septum.

Adverse effects of therapeutic use. Reported adverse effects of arsenic trioxide therapy in patients with acute promyelocytic leukaemia (APL) include leucocytosis, neutropenia, raised liver enzyme values, gastrointestinal disturbances, fatigue, oedema, hyperglycaemia, hypokalaemia, dyspnoea, cough, skin rashes, pruritus, pyrexia, headaches, paraesthesia, and dizziness. Prolongation of the QT interval and other cardiac arrhythmias have occurred. The so-called 'leukocyte activation syndrome' ('APL differentiation syndrome') similar to one that develops with tretinoin therapy (see Retinoic Acid Syndrome, p.1618) has occurred in some patients. Sudden death has been reported in a few patients.

◊ References,[1-8] including discussion of epidemic toxicity due to arsenic-contaminated drinking water.[4,6-8]

1. Health and Safety Executive. Inorganic arsenic compounds. *Toxicity Review 16*. London: HMSO, 1986.
2. Shannon RL, Strayer DS. Arsenic-induced skin toxicity. *Hum Toxicol* 1989; **8:** 99–104.
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Adulteration. Arsenical compounds have reportedly been used to "cut" cocaine and symptoms of arsenic poisoning may occur in cocaine abusers.[1] Toxicity due to the presence of arsenic in various ethnic remedies has also been reported.[2-4]

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