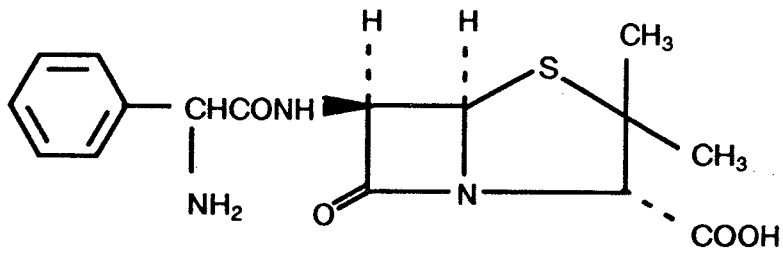
AMPICILLIN

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 69-53-4; 7177-48-2 (trihydrate); 69-52-3 (sodium salt)
Chem. Abstr. Name: 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, {2S-[2α, 5α, 6β(S*)]}-
Synonyms: Anhydrous: (2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; ampicillinum; ampicillinum anhydricum; anhydrous ampicillin; (6R)-6-(α-D-phenylglycylamino)penicillanic acid. Trihydrate: aminobenzylpenicillin ($3H_2O$); α-aminobenzyl-penicillin ($3H_2O$); ampicillinum trihydricum; (sodium salt) ampicillinnatrium; ampicillinum natricum

1.2 Structural and molecular formulae and molecular weight



$C_{16}H_9N_3O_4S$ Mol. wt: 349.40; 403.46 ($3H_2O$); 371.4 (sodium salt)

1.3 Chemical and physical properties of the pure substance

From Ivashkiv (1973), unless otherwise specified

(*a*) *Description*: White, crystalline powder; practically odourless; also occurs as trihydrate; pH of 10 g/ml aqueous solution, 3.5-6.0

(*b*) *Melting-point*: Ampicillin monohydrate melts with decomposition at 202°C; sodium ampicillin melts with decomposition at 205°C; sesquihydrate and anhydrous ampicillin decompose at 199-202°C. The melting range for ampicillin trihydrate with decomposition has been reported as 214.5-215°C and 202-204°C.

(*c*) *Optical rotation: Ampicillin monohydrate*, $[\alpha]_D^{21}$ +281° (c = 1 in H_2O); ampicillin sesquihydrate, $[\alpha]_D^{20}$ +283.1° (c in H_2O); sodium ampicillin $[\alpha]_D^{20}$ +209° (c = 0.2 in H_2O); anhydrous ampicillin $[\alpha]_D^{20}$ +287.9° (c = 1 in H_2O)

(*d*) *Solubility*: The solubilities of anhydrous ampicillin, ampicillin trihydrate and sodium ampicillin in various solvents are given in detail by Ivashkiv (1973).

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

(*f*) *Stability*: Ampicillin powders are stable when stored in a closed system at 43% and 81% relative humidity at room temperature for six weeks. Ampicillin is also stable at 35°C in such closed systems for nine weeks. Stability decreases significantly in the presence of sugars (Reynolds, 1989).

(*g*) *Dissociation constant*: pK_a = 2.5, 7.3 (23°C)

1.4 Technical products and impurities

Trade names: A-Cillin; Adobacillin; Aletmicina; Alpen; Alpen-N; Amblosin; Amcill; Amcill-S; Amfipen; Ampen; Amperil; Ampibel; Ampi-Biopharma; Ampibiotic; Ampibronc Capsules; Ampicil; Ampicillat; Ampicilline; Ampiciman; Ampicin; Ampicur; Ampifen; Ampi-Framan; Ampigal; Ampikel; Ampilag; Ampilan; Ampiland; Ampilar; Ampilean; Ampilisa; Ampilux; Ampinebiot; Ampinova; Ampinoxi; Ampi-Oral; Ampiorus; Ampipenix; Ampi-Rol; Ampisint; Ampi-Tablinen; Ampitex; Ampivax; Ampi-Vial; Ampixilion; Ampi-Zoja; Amplibios; Amplicid; Amplimedix; Amplipen; Amplipenyl; Ampliscocil; Amplital; Amplizer; Anhypen; Anidropen; Antibiopen; Anticyl; Apo-Ampi; Argocillina; Austrapen; Bemicina; Benusel Oral; Binotal; Bio-ampi; Biocellina; Bionacillin; Biosan; Bonapicillin; Bristin; Britapen; Britcin; Cilleral; Cimexillin; Citicil; Cuxacillin; Cymbi; D-Amp; Deripen; Diancina; Doktacillin; Domicillin; DuraAmpicillin; Espectrosira; Espimin-Cilina; Eurocillin; Famicillin; Farmampil; Fidesbiotic; Fortapen; Fuerpen; Germicillina; Geycillina; Globipen Balsamico; Gobemcina; Gramcillina; Grampenil; Guicitrina; Helvecillin; Hostes; Iwacillin; Lampocillina; Lifeampil; Marisilan; Maxicilina; Medicillin-D; Morepen; Napicil; NC Cilin; Negmapen; Novoexpectro; Nuvapen; Omnipen; Omnipen-N; Overcillina; Panbiotic; Panestes; Pen-A; Pen Ampil; Penampil; Pen A/N; Penberin; Pen-Bristol;

Penbristol; Penbritin; Penbritine; Penbrock; Pénicline; Penimaster; Penimic; Penimul; Peninovel; Penisint B.G.; Penisintex; Penorsin; Penrite; Pensyn; Pentrex; Pentrexil; Pentrexyl; Pentrexyl-K; Petercillin; Pharcillin; Platocillina; Plumericin; Poenbiotico; Polycillin; Prestacilina; Principen; Principen/N; Quimetam; Racenacillin; Radiocillina; Resan; Rivocillin; Rosampline; Roscillin; Saicil; Semicillin; Sernabiotic; Servicilline; Sesquicillina; Sintopenyl; SK-Ampicillin; SK-Ampicillin-N; Spectracil; Sumipanto; Supen; Suractin; Synpenin; Synthecillin; Tauglicolcinna; Togram; Tokiocillin; Tolimal; Totaciclina; Totacillin; Totacillin N; Totalciclina; Totapen; Trafarbiot; Trifacilina; Ukapen; Ultrabion; Urebion Ampicillina; Valmingina; Viacilina-A; Vidopen

The following names have been used for multi-ingredient preparations containing ampicillin, ampicillin salts and ampicillin trihydrate: Ampicin-PRB; Ampiclox; Ampicyn; Flu-Amp; Magnapen; Nuvapen Reard; Orbecilina; Penbritin KS; Pentrex-F; Polycillin-PRB; Principen with Probenecid; Pro-Biosan; Unasyn

USP anhydrous ampicillin contains 900-1050 μg/mg ampicillin (calculated as the anhydrous base), and the trihydrate contains 845-988 μg/mg. Ampicillin is available in 125-, 200-, 250- and 500-mg tablets that contain 90-120% labelled active ingredient, in 125-, 250- and 500-mg capsules containing 90-120% labelled active ingredient, and as oral suspensions of 100, 125 and 250 mg/5 ml containing 90-120% of the labelled active ingredient and probenecid. The sodium salt of ampicillin is available for injection in vials of 0.125, 0.25, 0.5, 1, 2 and 10 g.

Impurities of ampicillin that occur during preparation of the product are D-(-)-α-phenylglycine and 6-aminopenicillanic acid. It has been reported that sodium ampicillin in aqueous solution undergoes a reaction to form oligomeric products (Van der Bijl *et al.*, 1988).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

Ampicillin is produced by the acylation of 6-aminopenicillanic acid with D-(-)-α-phenylglycine by either microbiological or chemical synthesis (Ivashkiv, 1973). It was first marketed in 1961 in the UK. It is synthesized in Austria, Brazil, Hungary, India, Italy, Japan, the Republic of Korea, Mexico, the Netherlands, Romania, Spain, Sweden, Turkey, the USA and Yugoslavia (Chemical Information Services, 1989-90).

In Sweden, ampicillin sales in 1988 were 0.05 defined daily doses per 1000 inhabitants (Apoteksbolaget, 1988, 1989). In 1988, over six million new prescriptions of ampicillin were issued in the USA (La Piana Simonsen, 1989).

Ampicillin is not known to occur naturally.

2.2 Use

Ampicillin is bactericidal and has a similar mode of action to that of benzylpenicillin, although it has a broader spectrum of activity, covering several additional gram-positive and gram-negative organisms. Ampicillin may have a synergistic action with aminoglycosides and with the β-lactamase inhibitors clavulanic acid and sulbactam (Foulds, 1986; Barnhart, 1989).

The clinical indications for ampicillin cover a variety of infections, including those of the respiratory and urinary tracts, gonorrhoea, meningitis, septicaemia and enteric infections.

Expressed in various formulations as ampicillin equivalents, the usual oral dosing is 0.25-1 g every 6 h. The disposition of ampicillin is altered in pregnancy, and therefore higher doses may be required for severe infections in pregnancy (Assael *et al.*, 1979). Children may be given half the adult dose. The usual doses of ampicillin given by injection are 500 mg every 4 or 6 h intramuscularly (painful), by slow (5 min) intravenous injection or by intravenous infusion. Intrapleural, intraperitoneal and intrathecal injections of ampicillin are used occasionally (Reynolds, 1989).

2.3 Analysis

Ampicillin can be analysed in pharmaceutical preparations by microbiological, iodometric, colorimetric, high-performance liquid chromatographic (US Food and Drug Administration, 1988) and fluorometric assays (Barbhaiya & Turner, 1976) and by gas chromatography-mass spectrometry (Wu *et al.*, 1977). Ampicillin can be analysed in biological fluids by high-performance liquid chromatography (Miyazaki *et al.*, 1983; Haginaka & Wakai, 1987; Abuirjeie & Abdel-Hamid, 1988).

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

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F1 mice, seven to eight weeks of age, were administered ampicillin trihydrate (purity, 97%) by gavage at 0, 1500 or

3000 mg/kg bw in corn oil on five days per week for 103 weeks. The animals were maintained for a further one to two weeks, after which time they were killed. Weight gain was similar in all groups, and no significant difference in survival was observed in mice of either sex: at the end of the study period, 32/50, 21/50 and 20/50 males in the control, low-dose and high-dose groups, respectively, and 34/50, 27/50 and 28/50 females in the control, low-dose and high-dose groups, respectively, were still alive. In female mice, a slight increase in the incidence of benign lung tumours was observed (control, 1/50; low-dose, 0/50; high-dose, 4/50; $p = 0.049$, incidental tumour test). No increase in the incidence of any other neoplasm was recorded (National Toxicology Program, 1987; Dunnick *et al.*, 1989).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, seven to eight weeks old, were administered ampicillin trihydrate (purity, 97%) by gavage at 0, 750 or 1500 mg/kg bw in corn oil on five days per week for 103 weeks. Animals were observed for a further one to two weeks, after which time they were killed. Mean body weights of treated males and females were similar to those of controls. At the end of the study, 31/50, 27/50 and 26/50 control, low-dose and high-dose males, respectively, and 32/50, 31/50 and 31/50 control, low-dose and high-dose females, respectively, were still alive. An increase in the incidence of mononuclear-cell leukaemia was observed in treated males: control, 5/50; low-dose, 14/50 ($p = 0.019$, life-table test); high-dose, 13/50 ($p = 0.029$, life-table test; $p = 0.024$, life-table test for trend). A dose-related increase in the incidence of combined benign and malignant phaeochromocytomas of the adrenal medulla was also observed in males: control, 13/50; low-dose, 16/50; high-dose, 23/49 ($p = 0.007$, incidental tumour test; $p = 0.007$, trend test for incidental tumours). The incidences of mammary gland fibroadenomas in females were: control, 16/50; low-dose, 25/50 ($p = 0.019$, incidental tumour test); high-dose, 19/50. No increase in the incidence of tumours at other sites was observed (National Toxicology Program, 1987; Dunnick *et al.*, 1989). [The Working Group noted the high frequency of spontaneous tumours and that the increase in the incidence of mammary gland fibroadenomas was not dose-related.]

3.2 Other relevant data

(*a*) *Experimental systems*

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

Following intraperitoneal injection to rats, ampicillin was distributed throughout the major organ systems; the serum half-life was estimated to be 27 min (Fabre, 1977). Assay of serum collected after a single subcutaneous dose of sodium ampicillin at 10 mg/kg bw to guinea-pigs yielded ampicillin levels of approximately

10 μg/ml at 5 min, which fell rapidly to less than 0.2 μg/ml at 60 min (Young *et al.*, 1987).

(ii) *Toxic effects*

The intraperitoneal LD_{50} for ampicillin was 3300 mg/kg bw for one-day-old rats and 4500 mg/kg bw for 83-day-old rats (Goldenthal, 1971). The oral LD_{50} in rats was 10 g/kg bw and that in mice, 15.2 g/kg bw (Khosid *et al.*, 1975). Deaths occurred in 63, 45 and 100% of rabbits that received oral doses of ampicillin at 5, 15 and 50 mg/kg bw, respectively, for three consecutive days (Milhaud *et al.*, 1976).

Ampicillin administered as a single oral or subcutaneous dose of up to 5000 mg/kg bw had no noticeable toxic effect in mice or rats. Intravenous administration of 2000 mg/kg bw to mice caused muscle tremors, slowed respiration and mild convulsions. No biochemical, haematological or histological abnormality was seen in rats administered ampicillin at 100 or 500 mg/kg bw for 12 weeks (Brown & Acred, 1961). Administration of 25 mg/l in the drinking-water to four-week-old rats for up to eight weeks resulted in an increase in body weight gain; no toxic effect was noted (King, 1975).

Nabata *et al.* (1988) reported that intravenous exposures of rats to ampicillin at 1200 mg/kg bw per day for 28 days were well tolerated. Intravenous administration of sulbactam:ampicillin (1:2) at 90-1800 mg/kg bw for 28 days caused caecal enlargement; deposition of glycogen-like droplets in the liver occurred at the higher dose levels.

The toxicity of ampicillin trihydrate has been studied in Fischer 344/N rats and B6C3F1 mice (National Toxicology Program, 1987). In 14-day studies of rats and mice administered ampicillin at 200-2400 mg/kg bw by gavage, dose-related clinical signs included diarrhoea and excessive salivation in the high-dose rats immediately after dosing. Diarrhoea of minimal severity was observed in high-dose mice given 2400 mg/kg. No dose-related gross pathology or histopathology was observed in either species.

In 13-week studies, doses of 180-3000 mg/kg bw were administered by gavage on five days per week to rats and mice. All rats given 300 mg/kg bw and one of ten male mice at either 2000 mg/kg or 3000 mg/kg had diarrhoea. No compound-related pathology or histopathology was observed grossly in either species.

In the two-year studies (see section 3.1), ampicillin at doses of 750 or 1500 mg/kg bw (rats) and 1500 or 3000 mg/kg bw (mice) was administered by gavage on five days per week for 103 weeks. Clinical signs observed in treated rats included diarrhoea, excessive urination and chromodacryorrhoea; those in treated mice included increased salivation and decreased activity. The incidence of C-cell hyperplasia of the thyroid gland was increased in low-dose male and high-dose female rats. High-dose male rats showed increased incidences of hyperkeratosis

and acanthosis of the forestomach. In male and female mice, an increased incidence of forestomach lesions, including ulcers, inflammation, hyperkeratosis, acanthosis and evidence of fungal infection, was observed in exposed animals.

(iii) *Effects on reproduction and prenatal toxicity*

The absence of experimental details precluded assessment of the only study of prenatal toxicity (Korzhova *et al.*, 1981).

(iv) *Genetic and related effects*

Ampicillin induced lysogenic phage in *Staphylococcus aureus* (Manthey *et al.*, 1975). It did not induce a SOS response in *Escherichia coli* PQ37 (Venier *et al.*, 1989), and no differential toxicity was observed in *E. coli* in the absence (Green & Tweats, 1981) or presence of an exogenous metabolic system (Tweats *et al.*, 1981; De Flora *et al.*, 1984). In *Salmonella typhimurium* plate incorporation tests, ampicillin was not mutagenic in the presence or absence of an exogenous metabolic system (De Flora *et al.*, 1984; Mortelmans *et al.*, 1986; National Toxicology Program, 1987).

Treatment of *Vicia faba* seeds with a 0.5% solution of ampicillin led to chromosomal aberrations in root-tip meristem cells (Prasad, 1977).

Ampicillin did not induce mutation at the *tk* locus in L5178Y mouse lymphoma cells in the presence or absence of an exogenous metabolic system at concentrations up to 5000 μg/ml (National Toxicology Program, 1987). No increase in the frequency of sister chromatid exchange was observed in Chinese hamster CHO cells with concentrations of ampicillin up to 1500 μg/ml in the presence or absence of an exogenous metabolic system (National Toxicology Program, 1987). Ampicillin did not induce sister chromatid exchange in human lymphocytes *in vitro* (Jaju *et al.*, 1984). No chromosomal aberration was observed in Chinese hamster CHO cells treated with ampicillin at 0-1500 μg/ml in the presence or absence of an exogenous metabolic system (National Toxicology Program, 1987). Ampicillin did not induce chromosomal aberrations in human fibroblasts after 50 h of treatment with a concentration of 4000 μg/ml (Byarugaba *et al.*, 1975), but a dose of 28 μg/ml induced chromosomal aberrations in human peripheral lymphocytes *in vitro* (Jaju *et al.*, 1984). [The Working Group noted the low concentration used in this test, as compared to those of other reports.] It was reported in an abstract that ampicillin did not induce chromosomal aberrations in human lymphocytes *in vitro* at concentrations up to 10 mg/ml (Stemp *et al.*, 1988).

It was reported in an abstract that ampicillin at single- or double-dose oral regimens of 5 mg/kg did not induce micronuclei in rats treated *in vivo* (Stemp *et al.*, 1988).

(*b*) *Humans*

(i) *Pharmacokinetics*

The pharmacokinetics of ampicillin have been reviewed (Barza & Weinstein, 1976).

Ampicillin is relatively stable in the acid contents of the stomach; anhydrous or trihydrated ampicillin is absorbed incompletely from the gut after oral administration. Peak concentrations in plasma (2-6 mg/l after an oral dose of 500 mg) occur within 1-2 h. Ester prodrugs (pivampicillin, bacampicillin) and the condensation prodrug (hetacillin) of ampicillin are absorbed more readily than ampicillin (Jusko & Lewis, 1973; Loo *et al.*, 1974; Magni *et al.*, 1978; Pennington & Crooks, 1983). Ampicillin at 500 mg given by intramuscular injection as the sodium salt produced plasma peaks of 7-14 mg/l within about 1 h (Doluisio *et al.*, 1971).

Ampicillin is distributed widely, and therapeutic concentrations can be achieved in soft tissues, including ascitic, pleural and joint fluids (Lewis & Jusko, 1975). Bacampicillin produces higher tissue concentrations than ampicillin (Bronsveld *et al.*, 1978). Only 20% of ampicillin is bound to plasma proteins (Barza & Weinstein, 1976). It crosses the placenta (Hirsch *et al.*, 1974; Kraybill *et al.*, 1980), and detectable concentrations of ampicillin occur in the milk of nursing mothers (Chow & Jewesson, 1985).

Ampicillin is excreted *via* renal glomerular and tubular routes in the urine; its plasma half-time is usually 1-2 h (Sjövall, 1985) but is longer in elderly people (Triggs *et al.*, 1980). In patients with renal failure, the half-time was as long as 20 h (Hori *et al.*, 1983).

Healthy subjects metabolize about 20% of a given dose (250-500 mg) of ampicillin. Within 12 h, 7% of the total dose is excreted as metabolites in urine (Cole *et al.*, 1973; Haginaka & Wakai, 1987). Ampicillin is metabolized to 5R,6R-penicilloic acid and 5S,6R-penicilloic acid (Bird *et al.*, 1983) and to piperazine-2,5-dione after oral intake (Haginaka & Wakai, 1987). Other, unidentified metabolites have been reported (Masada *et al.*, 1979).

(ii) *Adverse effects*

Skin rashes (Almeyda & Levantine, 1972) are the most common side-effects of ampicillin treatment and are either urticarial or maculopapular. The allergic nature of the maculopapular rash is uncertain (Bierman *et al.*, 1972; Campbell & Soyka, 1977; Sokoloff, 1977; van Ketel, 1984). Non-allergic fever due to ampicillin occurs rarely (Mackowiak & LeMaistre, 1987). The overall incidence of skin reactions among a group of patients who received the drug between 1975 and 1982 was 59/1775 (3.3%) (Bigby *et al.*, 1986), although higher incidences have been reported. Unusually high incidences of skin rashes occur during treatment with

ampicillin of glandular fever and lymphatic leukaemia (Cameron & Richmond, 1971; Lambert *et al.*, 1972).

Ampicillin commonly affects the gastrointestinal tract, at least in children (25-35%) (Feder, 1982). It has been reported to be one of the drugs most frequently associated with pseudomembranous colitis (Gorbach, 1987). Seizures have been reported after use of ampicillin in cases of underlying cerebral dysfunction (Serdaru *et al.*, 1982) or concomitant renal insufficiency resulting in high serum concentrations of ampicillin (Hodgman *et al.*, 1984).

(iii) *Effects on reproduction and prenatal toxicity*

In a study of 280 000 women belonging to a prepaid health plan in Seattle, WA (USA), all drug prescriptions and all pregnancy outcomes were monitored between July 1977 and December 1979. Among the liveborn babies of 6837 women, 80 (1.2%) had major congenital malformations. Four infants born to 309 women for whom ampicillin had been prescribed in the first trimester had major malformations [types not specified], giving a prevalence of 13 per 1000, which was not significantly different from the overall prevalence in the total population studied (12 per 1000) (Jick *et al.*, 1981).

In a second study of the same population covering January 1980 to June 1982, 6509 women had pregnancies ending in livebirths, and 105 (1.5%) of these had major congenital malformations. Three infants born to 409 women for whom ampicillin had been prescribed in the first trimester had major malformations [types not specified], giving a prevalence of seven per 1000, compared with an overall prevalence in the entire group of 15 per 1000 (Aselton *et al.*, 1985).

In a hospital study of Australian women, 7371 mothers had singleton pregnancies in 1978-81; 1060 of them had used amoxycillin or ampicillin [not recorded separately] at some time during pregnancy: 211 had been treated in the first trimester only and 73 in the first trimester and later. It was stated that there was no evidence of any association between use of these drugs and the incidence or type of congenital malformations, which were observed in 12 of the 284 (4.2%) exposed babies, compared with the nonexposed (297/6311, 4.7%). There was no association with use of these drugs and intrauterine growth retardation or perinatal death, but there was a significant ($p < 0.01$) difference in the rate of prematurity in the users (8.9%) compared with nonusers (6.5%), which was not due to age or differences in use of alcohol. There was also a significant ($p < 0.0001$) increase in the prevalence of low-birth-weight (< 2.5 kg) babies among users (9.6%) compared with nonusers (6.6%), which was still significant ($p < 0.05$) when controlled for length of gestation (Colley *et al.* 1983). [The Working Group noted that the effects might have been due to underlying infection in the mothers.]

(iv) *Genetic and related effects*

No adequate study was available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

One case each of lymphoproliferative disease and Kaposi's sarcoma has been reported in association with use of ampicillin (Gordon & Luk, 1982; Brenner *et al.*, 1984).

Ampicillin was included in a hypothesis-generating cohort study designed to screen a large number (215) of drugs for possible carcinogenicity, which covered more than 140 000 subscribers enrolled in July 1969 to August 1973 in a prepaid medical care programme in northern California (USA). Computer records of persons to whom at least one drug prescription was dispensed were linked to cancer records from hospitals and the local cancer registry. Observed numbers of cancers were compared with expected numbers, standardized for age and sex, derived from the entire cohort. Three publications have summarized the screening findings for follow-up periods of up to seven years (Friedman & Ury, 1980), nine years (Friedman & Ury, 1983) and 15 years (Selby *et al.*, 1989). [The Working Group chose to omit mention of associations based on fewer than three cases.] Among 6706 persons who received ampicillin, an association was noted with subsequent skin cancer (four cases observed, 0.9 expected; $p < 0.05$) in the seven-year report. In the 15-year report, an association was noted with lung cancer (48 cases observed, 27.3 expected; $p < 0.002$). The latter association, although apparently not explained by cigarette smoking in an analysis of smoking habits carried out specifically for people taking ampicillin, was also seen for several other antibiotics. [The Working Group noted, as did the authors, that, since some 12 000 comparisons were made in this hypothesis-generating study, the associations should be verified independently. Data on duration of use were not provided.]

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Ampicillin is a broad-spectrum antibiotic and has been used extensively to treat bacterial infections since 1961.

4.2 Experimental carcinogenicity data

Ampicillin was tested for carcinogenicity by oral administration in mice and rats. It increased the incidences of mononuclear-cell leukaemia and of

phaeochromocytomas of the adrenal medulla in male rats. A slight increase in the incidence of benign lung tumours was observed in female mice.

4.3 Human carcinogenicity data

In a hypothesis-generating cohort study, use of ampicillin was associated with the occurrence of lung and skin cancers, but these findings could have been due to chance.

4.4 Other relevant data

Use of ampicillin during the first trimester of pregnancy has not been associated with an increase in the incidence of major congenital malformations.

Ampicillin increased the frequency of chromosomal aberrations in human lymphocytes but not in human fibroblasts *in vitro*. It did not induce chromosomal aberrations in Chinese hamster cells, mutations in mouse lymphoma cells or sister chromatid exchange in human lymphocytes or in Chinese hamster cells. Ampicillin induced chromosomal aberrations in *Vicia faba*. It was not mutagenic to *Salmonella typhimurium* and did not induce differential toxicity in *Escherichia coli* strains. (See Appendix 1.)

4.5 Evaluation[1]

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

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

Overall evaluation

Ampicillin *is not classifiable as to its carcinogenicity to humans (Group 3).*

5. References

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[1]For description of the italicized terms, see Preamble, pp. 26–29.

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