NR 2004:6

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

134. Penicillins

Gregory A. Moore and Olle Nygren

Nordic Council of Ministers

ARBETE OCH HÄLSA | VETENSKAPLIG SKRIFTSERIE

ISBN 91-7045-712-3 ISSN 0346-7821

Arbetslivsinstitutet
National Institute for Working Life

Arbete och Hälsa

Arbete och Hälsa (Work and Health) is a scientific report series published by the National Institute for Working Life. The series presents research by the Institute's own researchers as well as by others, both within and outside of Sweden. The series publishes scientific original works, dissertations, criteria documents and literature surveys.

Arbete och Hälsa has a broad target-group and welcomes articles in different areas. The language is most often English, but also Swedish manuscripts are welcome.

Summaries in Swedish and English as well as the complete original text are available at www.arbetslivsinstitutet.se/ as from 1997.

ARBETE OCH HÄLSA
Editor-in-chief: Staffan Marklund
Co-editors: Marita Christmansson, Birgitta Meding, Bo Melin and Ewa Wigaeus Tornqvist

National Institute for Working Life
S-113 91 Stockholm
Sweden

ISBN 91–7045–712–3
ISSN 0346–7821
http://www.arbetslivsinstitutet.se/
Printed at Elanders Gotab, Stockholm

Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway, and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following members:

Gunnar Johanson (chairman)	Karolinska Institutet and National Institute for Working Life, Sweden
Vidir Kristjansson	Administration of Occupational Safety and Health, Iceland
Kai Savolainen	Finnish Institute of Occupational Health, Finland
Vidar Skaug	National Institute of Occupational Health, Norway
Karin Sørig Hougaard	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as HSELINE, Medline and NIOSHTIC. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee on Occupational Standards is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access is used.

The document aims at establishing dose-response/dose-effect relationships and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on penicillins was made by Dr Gregory Moore, the Swedish Chemicals Inspectorate and Dr Olle Nygren, the National Institute for Working Life, Sweden. The draft document was discussed within the Expert Group and the final version was accepted by the Nordic Expert Group April 20, 2001, as its document. Editorial work and technical editing was performed by the Group's Scientific Secretaries, Jill Järnberg and Anna-Karin Alexandrie, at the National Institute for Working Life in Sweden.

All criteria documents produced by the Nordic Expert group may be downloaded from *www.nordicexpertgroup.org*.

We acknowledge the Nordic Council for its financial support of this project.

Abbreviations

BPO	benzylpenicilloyl
HPLC	high performance liquid chromatography
KPG	crystalline potassium penicillin G
OECD	Organisation for Economic Co-operation and Development
SI	stimulation index
TLV	threshold limit value

Contents

1. Introduction

Penicillins are a class of antibiotic produced by some members of the genus *Penicillium* (14, 45). In brief, in 1929 Fleming discovered penicillin and recognised its antibacterial properties (25). Penicillin and derivatives were produced by fermentation by the end of the 1940s. The penicillin family of compounds, however, has been a significant source of in-plant medical problems since their large scale production began in the late 1940s (83). Medical problems have also occurred in other occupations due to inhalation and dermal exposure (19, 29, 90).

This document considers sensitisation in workers occupationally exposed to manufactured penicillins by the inhalation and dermal routes. To determine all the possible different types of penicillins that may give rise to occupational exposure in the Nordic countries all of the penicillin containing products available on the USA and UK markets were compared with those found on the Swedish market. Most of the USA and UK products were found on the Swedish market. Hence, to rationalise this criteria document, products on the Swedish market are used as a surrogate for all Nordic countries. It is, however, recognised that for the purpose of risk reduction and/or management at that time, an exact itinerary of all products on each Nordic country's market may be more relevant.

Adverse effects observed in patients (general public) exposed *via* inhalation and dermal exposure routes are also considered when deemed relevant. Type II and III hypersensitivity are not addressed in this document, as they are apparently associated with other routes of exposure e.g. oral, intravenous. Similarly, only information from animal experiments conducted by the inhalation and dermal routes are considered: animal experiments performed by other routes are often conducted for clinical and pharmacological research purposes. It is also assumed that, since penicillins are registered pharmaceutical and veterinarian preparations used for the treatment of bacterial infections, additional unpublished information must be available to have satisfied the different regulatory requirements for registration of penicillins by exposure routes both currently used and discontinued. Administration of penicillins by topical and inhalatory routes is not currently approved, as hypersensitivity effects have been demonstrated in man.

2. Substance identification and physical and chemical properties

Penicillins can be classified in several ways. Either as natural or synthetic or with regard to their resistance to acids or penicillinases or as having more or less broad spectrum properties (10). The penicillins have a fused ß-lactam thiazolidine ring system in common. It is known as 6-aminopenicillanic acid, and vary in the amino (R1) and carboxylic (R2) side chains (Figure 1).

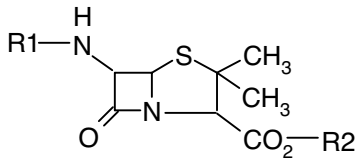


Figure 1. The general structure of penicillins.

The inherent strain of the N-atom in the four membered ß-lactam ring and the distortion of the planar geometry in the bicyclic system are commonly regarded as an essential factor to the high reactivity of penicillins and contributing to their antibacterial properties. Besides the ß-lactam ring, the side chains are important factors, essential for the biological activity. The dissociation constant (pKa) for penicillins is about 2.6-2.8 (37), which indicates a fairly strong acidity. Information regarding other physical properties of penicillins has been presented by Florey, Van Krimpen *et al*. and Hou *et al*. (27, 37, 86).

In the activity and degradation of penicillins the ß-lactam ring plays an essential role. In neutral or alkaline medium, the ring can be opened either by hydroxide ions or by other nucleophils. Both reaction paths lead *via* different intermediates to penicilloic acid (86). Usually the rates of alkaline hydrolysis are significantly larger than those of acid hydrolysis (37). Transition metals ions (e.g. Cu^{2+}) cause a very large increase in the rate of aminolysis and hydrolysis of penicillins.

Penicillins are used for treatment of a large number of bacterial infections in humans and animals (4). The primary mechanism of action is inhibition of the bacterial cell wall synthesis. Penicillins have a structural analogy of the ß-lactam ring with D-alanyl-D-alanine, which terminates free *N*-acetylmuramic acid, a part of the glycan structure of the bacterial cell wall. Gram-positive bacteria are more sensitive to penicillin than gram-negative bacteria as they have higher glycan content (up to 50% *cf*. 1-10%)(86).

3. Occurrence, production and use

3.1 Volumes - production, export, import, and use

Penicillin is produced and handled in the Nordic countries but because penicillin is registered as a pharmaceutical and veterinarian product information concerning production, use, import and export volumes is confidential information in the Nordic countries and thus cannot be detailed in this document. However, there are some published information on the use of penicillins in humans and animals.

The sales of penicillin for human use in Sweden during 1999 were 8.1 daily doses per 1 000 inhabitants (3).

Total usage of penicillins in animals in Sweden between 1988 and 1993 has been documented by Björnerot and Tysén (9). In 1993, 13.2 tonnes of benzylpenicillin (Table 1 and Appendix 1) were used compared to 11.6 tonnes in 1988. On average 97% of benzylpenicillin was injectable. Also in 1993, 0.86 tonnes of

ampicillin/amoxycillin (Table 1 and Appendix 1) were used, an increase from 0.65 tonnes in 1988.

3.2 Production and use

There are six naturally occurring penicillins, but only benzylpenicillin (Penicillin G; Table 1 and Appendix 1), and phenoxymethylpenicillin (Penicillin V; Table 1 and Appendix 1) are widely used as anti-infective agents. The ß-lactam base is microbiologically produced (86) and is subsequently used to produce derivatised penicillins (Table 1 and Appendix 1).

In the production of penicillin by fungi *Penicillium chrysogenum*, many biological, chemical, and technical factors influence the growth of the cells and product formation. Synthesis of β-lactam-antibiotics is a complex reaction system coupled with both catabolism and anabolism, and undergoes various kinds of metabolic regulation (8). Because bacteria may develop resistance to penicillins used in treatment, different penicillin analogues have been developed to overcome this problem and extend the antibiotic spectrum (86). Consequently, there are a large number of antibiotics available requiring different processes for formation. Intermediate use of penicillin bases for the production of penicillin derivatives by chemical synthesis is in this document not regarded as use but as production of penicillins. This may be a captive intermediate use i.e. on the same site of production by a near by sister company, or by a second-site. The use of penicillin derivatives in the production of end-products by formulation is also regarded as production of penicillins rather than use. This may occur on-site or at a secondary site. Handling activities are also regarded as production, e.g. packaging. It has, however, not been possible to obtain data on the number of sites where penicillins are produced, as there are no site-specific details available for any of the production units in the Nordic countries.

Several derivatised penicillins are currently registered for use in Sweden. Table 1 shows the penicillins, with commonly used trivial name, CAS number, molecular formula, and weight, currently registered by Medical Products Agency in Sweden (54). Appendix 1 contains more comprehensive information regarding physical and chemical properties for these penicillin derivatives.

For human use, types of penicillin preparations that are currently used include oral solids (tablets, capsules), and oral solutions (mixtures, drops, injectibles, infusions). In the past, ointments, powders, sprays, lozengers, suppositories, and vaginal bougies have been used (56, 57, 88). For animal use, penicillins are used in tablets, mixtures, injections, and intra-mammary preparations. In the Nordic countries penicillins are prescription drugs and cannot be obtained by across-the-counter sales. In Sweden, given to animals penicillins are only allowed to be used for medication and not as growth stimulation or for prophylactic purposes.

Table 1. Penicillin derivatives currently used in Sweden (54).

Trivial name	CAS number	Molecular formula	Molecular weight
Procaine benzylpenicillin	54-35-3	$C_{16}H_{18}N_2O_4S.C_{13}H_{20}N_2O_2.$	571
Ampicillin sodium salt	69-52-3	$C_{16}H_{19}N_3O_4S.Na$	372
Benzylpenicillin sodium salt	69-57-8	$C_{16}H_{18}N_2O_4S.Na$	357
Penicillin V potassium salt	132-98-9	$C_{16}H_{18}N_2O_5S.K$	389
Cloxacillin sodium salt	642-78-4	$C_{19}H_{18}ClN_3O_5S.Na$	459
Benethamine penicillin	751-84-8	$C_{16}H_{18}N_2O_4S.C_{15}H_{17}N$	546
Penicillin G benzathine	1538-09-6	$(C_{16}H_{18}N_2O_4S)_2.C_{16}H_{20}N_2$	909
Penicillin G diethylaminoethyl ester	3689-73-4	$C_{22}H_{31}N_3O_4S$	434
Procaine penicillin	6130-64-9	$C_{16}H_{18}N_2O_4S.C_{13}H_{20}N_2O_2.H_2O$	589
Cloxacillin sodium monohydrate	7081-44-9	$C_{19}H_{17}ClN_3O_5S.Na.H_20$	476
Dicloxacillin sodium salt hydrate	13412-64-1	$C_{19}H_{16}Cl_2N_3O_5S.Na.H_2O$	510
Globacillin	17243-38-8	$C_{16}H_{17}N_5O_4S$	375
Pivampicillin hydrochloride	26309-95-5	$C_{22}H_{29}N_3O_6S.HCl$	500
Pivamdinocillin	32886-97-8	$C_{21}H_{33}N_3O_5S$	440
Selexid	32887-01-7	$C_{15}H_{23}N_3O_3S$	325
Pivmecillinam hydrochloride	32887-03-9	$C_{21}H_{33}N_3O_5S.HCl$	476
Ampicillin pivaloyloxymethyl ester	33817-20-8	$C_{22}H_{29}N_3O_6S$	464
Becampicillin hydrochloride	37661-08-8	$C_{21}H_{27}N_3O_7S.HCl$	502
Flucloxacillin	58486-36-5	$(C_{19}H_{16}ClFN_3O_5S)_2.Mg.8H_2O$	1 074
Amoxicillin trihydrate	61336-70-7	$C_{16}H_{19}N_3O_5S.3H_2O$	419

4. Occupational exposure data

4.1 Environmental monitoring

Data on quantitative monitoring of penicillins in work place air are few. In three studies personnel air monitoring have been conducted: two in the USA determining total and respirable penicillin dust in the work place during manufacture and one in Sweden determining respirable dust during the preparation of an oral solution at the pharmacy.

Hanke and Patnode studied the total and respirable dust in a penicillin drug factory (32). The total dust concentration was determined using pre-weighed membrane filters and the respirable dust was collected using a 10 mm cyclone with a flow rate of 1.7 litres/minute. The result showed dust levels not exceeding the threshold limit value (TLV) for various dust types. Shmunes *et al*. surveyed penicillins in a factory and determined the total dust concentration by sampling on membrane filters with a pore size of 0.8 μm (83). They did not report marked levels in comparison with the various TLVs for different types of dust (83).

In a study conducted at the Central Laboratory of the National Corporation of Swedish Pharmacies, the emission of dust was investigated during preparation of penicillin formulations (26). The particle size distribution and airborne dust levels were measured during preparation of Imacillin® and Pondicillin®. The monitoring was conducted during the preparation of a penicillin solution for 5 minutes. The particle size characterisation showed that the dust had a particle size below 3 μm. The airborne emission was determined for Imacillin® by sampling on membrane filter and analysis by traditional microbiology technique. The average level of Imacillin® was 1.2 $\mu g/m^3$/5 minutes sampling (range 0.69-2.9) (26).

A semi-quantitative method using Petri dishes inoculated with test organisms on agar gel has been used to survey airborne antibiotics in the manufacturing workplace (61). The bacterial strain used was *Bacillus stearothermophilus* var. *calido lactis*. The Petri dishes were placed out at different work areas during each work episode, which could have a duration of one to five hours. After exposure at the work areas the Petri dishes were incubated and inspected. To determine that growth inhibition was specifically due to penicillins and thus minimise false positives being included, one half of each plate was treated with penicillinase. The number of inhibition zones was recorded to determine the degree of exposure: <5/20 inhibition zones was classified as "low exposure" and >5/20 inhibition zones as "high exposure" (61).

No others reports on specific studies of airborne penicillins have been found. All the studies above lack specificity since correlation calculations between airborne penicillins and health effects have been based on the total or the respirable dust level assuming all dust emanates from penicillins. In some cases this assumption may be adequate, e.g. in pharmaceutical industry production situations where the only dust source is during the handling of dry penicillins. However, in many other cases such an assumption would not be acceptable since there would be significant misjudgement of the airborne penicillin concentration from the total dust or respirable dust level. The lack of reliable studies on airborne penicillins emphasises the need for the development of new robust methods for measuring penicillins in workplace air.

4.2 Groups occupationally exposed

Present day exposure information relevant for different occupational groups in the Nordic countries either does not exist or is not available in a published form for assessment in this document. It is, therefore, not possible to estimate the number of workers that may be exposed to penicillins and the extent of their exposure. However, several occupational groups potentially exposed to penicillins are postulated. The possibility also exists that other groups of workers, not identified in this assessment, may be exposed to penicillins. For instance, exposure may occur when handling penicillin contaminated materials such as hospital laundry, medical waste and other waste disposal.

Penicillin is a solid powder that can form dusts during handling. Also solutions of water soluble and insoluble penicillins are prepared. Formation of aerosols of

penicillins would also be expected. Penicillin's vapour pressure is very low, however, it is possible that a low level of exposure from the gas phase may occur – the characteristic odour of many penicillins is distinct. Hence, the main forms of penicillin that will result in exposure are dust, solutions, and aerosols. However, due to the sensitivity of some individuals it cannot be ruled out that penicillin vapours may elicit reactions in sensitised individuals.

Several occupational groups may be exposed to penicillin:
Workers producing penicillin and end-products are likely to be exposed to penicillin in different physical forms mainly *via* the inhalation and dermal routes. Exposure would be expected to occur during fermentation, chemical synthesis of derivatives and formulation of end-products. The fermentation process may result in exposure to penicillin dusts, solutions, and aerosols during routine procedures such as loading, sampling, maintenance, packing, storage etc. In a review by Naumann and Sargent (67), the potential dust exposure for each worker task during the handling of bulk pharmaceuticals has been estimated (Table 2). Exposure during chemical synthesis of derivatives may also result in exposure during different work activities that may be similar to those during fermentation. Formulation of end-products is envisaged to result in several different exposure situations due to the diversity of products that can be prepared. However, when ready-to-sale end-products are handled, exposure is not expected to occur from intact packages handled following recommended procedures.

Table 2. Total dust levels in the pharmaceutical industry. Adapted from (67).

Work task	Air concentration (mg/m^3)
Dumping from drums	0.9
Dumping from bags	1.2
Scooping out of drums	0.8
Filling drums from a blender	0.6
Bin transfers	0.2
Digging centrifuge	0.3
Milling	2.3
Tray dumping	2.7
Film coating	0.1
Sieving	0.8
Granulating	0.9
Compressing	0.08
Packaging	0.01
Sampling	0.01
Encapsulating	0.05

Pharmacists are expected to be exposed during the preparation of penicillin. solutions (i.e. mixtures and drops). Information detailed in Appendix 2 and reference (54) shows that several penicillin solutions have to be prepared by the pharmacists prior to use by the public. During the preparation procedure inhalation and dermal exposure to powdered penicillins may occur. Dermal exposure to penicillin solution cannot be ruled out. Indeed, Kobayashi details that pharmacists have reported an increase in allergy-like symptoms that were related to the inhalation of pharmaceutical dusts (50). Furthermore, Flink *et al.* demonstrated measurable Imacillin® dust during the preparation of a penicillin formulation conducted at Central Laboratory of the National Corporation of Swedish Pharmacies (26).

Published data indicate that health-care-personnel (e.g. nurses and possibly doctors) may be exposed primarily by the dermal route due to accidental spills/ leaks during preparation/administration of injectibles. Administration of other penicillin solutions may also result in exposure. It cannot be ruled out that exposure may occur during non-routine practices such as the manual grinding of penicillin solids with or without liquid dispersion to facilitate the ease of administration to the elderly and other patient groups. Exposure may also occur when preparing injectible and infusion preparations if the procedures are not strictly conducted under "closed-system" conditions. Different potential exposure patterns between in-clinics and out-clinics are also probable. It is also important to consider that stress, working conditions, and technical facilities may influence exposure to penicillins.

Veterinary workers in Nordic countries may be accidentally exposed to spills/ leaks, during preparation/administration of penicillin solutions. Exposure may also occur during the disposal of syringes under out-clinic conditions. Frequent exposure of veterinarians may occur during administration of "intra-mammary penicillins" for the treatment of infected cow udders (mastitis). Respiratory, dermal, and eye exposure to penicillin residues bound on detached animal skin and hair may occur. It is also important to consider that the working conditions of a veterinarian on out-clinic duties are extremely variable depending on the work location setting (e.g.farm) and type of animals to be treated (e.g. agricultural, reared, domestic, fishery). Because of these variables, stress is expected to influence the potential exposure to penicillin.

Agricultural workers may be exposed to penicillins as they perform the administration of penicillin preparations to livestock during the treatment period. Exposure to penicillin residues bound on detached animal skin and fur may occur. Exposure *via* excreta, waste cows´ milk during the withdrawal period, and other sources cannot be ruled out.

Fishery workers may be exposed to penicillins during large scale spraying. Exposure to aerosolised penicillins may occur by inhalation and dermal contact.

Because penicillin is routinely used in laboratories as a bacteriostate and in some instances for research, exposure of laboratory personnel is likely.

The general public (non-occupational exposed population) is also considered here, as occupationally exposed workers are also the general public and may be

exposed through the use of medicines containing penicillin. In 1946, Friedlaender pointed out that, occupational dermatitis may be more prevalent in workers receiving topical therapies of penicillin (29). This conjecture may have also been extended to respiratory effects because of the use of aerosolised penicillin as a treatment. Although topical and inhalatory penicillins are no longer available it is of interest that preparations of penicillins are available to the general public in the powdered form. These are sold as single dose preparations intended for preparation of a solution by the patient (54). Hence, there is the possibility that inhalatory and skin exposure may occur. It is also possible that dermal exposure of adult workers to penicillin solutions intended for children may occur due to accidental spills during handling of the solution and the expectorating reaction of children unwilling to swallow the medicine. It is also important to consider that workers are indirectly exposed *via* the environment to e.g. food commodities that may contain penicillin residues: the study by Naclerio *et al*. (66) demonstrated that a penicillin sensitised nurse elicited hypersensitivity symptoms on consumption of certain foods. Aguis *et al*. commented that there may be evidence of allergic sensitisation to a therapeutic substance as a result of occupational exposure to the substance (1). Therefore, the reverse must also be considered.

Based on the above it is expected that the main routes of occupational exposure to penicillins will be *via* inhalation and dermal exposure to powders, solutions, and aerosols. However, oral exposure and exposure to penicillin vapour may occur. Oral exposure of workers in the non-occupational situation may have to be considered when taking medications. Thus, multiple pathways of exposure of different populations have to be considered as different sources and portals of entry that may contribute to exposure under different situations. It is also necessary to take into account variations in exposure levels. The exposure during the sensitisation and elicitation phases in immunologically mediated hypersensitivity may be spatially, temporally, and quantitatively different.

In summary, the occupational groups that are potentially exposed to penicillins include:

- workers involved in the manufacture, processing and formulation including handling of penicillins.
- pharmacists preparing formulations of penicillins.
- health-care-personnel administering penicillins to humans and possibly preparing formulations.
- veterinarians preparing formulations and administering penicillins to animals.
- agricultural workers using/administering penicillins in connection with animals and exposure from animal waste and products.
- fishery workers using penicillins on fishery farms.
- laboratory workers using penicillins for research purposes.
- workers exposed to penicillins at work, *via* the use of medications, and in the non-occupational environment.

5. Measurement and analysis of workplace exposure

5.1 General

Analytical methods for the detection of penicillins may be classified into two broad groups:

– immunological and microbiological techniques which respond to groups of penicillins but do not discriminate among them (screening methods), and
– compound-specific methods, involving chemical or physical separation of the specific drug from other components for the detection, identification and discrimination among different penicillins (chromatographic methods).

5.2 Screening methods

Screening test methods for the detection of penicillin residues include the classical microbial inhibition tests, such as the Swab test, the antibiotic and sulfa test, the inhibition tests based on colorimetry, such as the Brilliant Black reduction test, and the immunological assays, such as the enzyme-linked immunosorbent assays (ELISA) and the Charm test II receptor assay (10). These screening test methods are usually sensitive to penicillin G (benzylpenicillin), with a detection capacity down to the ng/g concentration range. They also provide fairly reliable test results, are relatively simple, inexpensive, and require simple equipment. However, they lack compound specificity and are, at the best, semi-quantitative, and are therefore only suitable methods when solely qualitative information is desired, e.g. screening for presence of penicillins.

Some other screening methods, described by British, European and US Pharmacopoeia are Ph. Eur. ed. 2 assay, which is based on mercurimetric titration, BP 80 assay, which is based on imidazole-mercury(II) spectrometry and/or iodometric titration and USP XXI assay scheme, which is based on a number of methods depending on the penicillins tested for, e.g. iodometric titration, hydroxylamine-ferric ion colorimetry. Some specific spectroscopic screening methods have also been used (86), e.g. by labelling the penicillins with a fluoropore, such as fluorescamine, α-amino group containing penicillins can be detected down to 20 ng/ml. Other traditional fluorescence derivatives, e.g. dansyl chloride, were proved to be too unstable to be useful. Penicillins have no native distinctive UV-absorption above 220 nm, but by employing a nucleophilic attack on the ß-lactam ring by an imidazole or triazol, an UV-absorbing derivate is formed and can be used in an UV-spectrometric assay for penicillins (86).

5.3 Chromatographic methods

High performance liquid chromatography (HPLC) with reversed phase columns or ion-pair reversed phase columns have extensively been used for separation of penicillins (10, 59). For most applications a sample preparation step is needed prior to the HPLC analysis. The extent of sample pre-treatment depends on the

origin of the sample and can be anything from a simple dissolution to a multi-step extraction and pre-concentration scheme. For determination of penicillin residues in food stuff a number of sample pre-treatment procedures have been described (10), e.g. protein precipitation procedures, solvent extraction and pre-concentration procedures, adsorption-elution clean-up procedures, and solid-phase extraction procedures. Of these techniques solid-phase extractions are regarded as state-of-the-art and offers both a simple and robust sample clean-up as well as the possibility to obtain at least a 10-fold concentration of the analytes. Different derivatisation techniques have been employed and may decrease the detection limit by 5-10 times (10, 59, 86). Mass spectrometry (MS) offers specific and selective detection of penicillins and HPLC-MS has been used for the determination of specific penicillins and their metabolites (10).

6. Toxicokinetics

Location of first hand references dealing with the toxicokinetic behaviour of penicillins is few. However, second-hand information without details of source-references is detailed in Wright (90) and Martindale (56). These two sources mainly concern pharmacological studies conducted by the oral and parenteral (intravenous and intramuscular) routes. In some cases the route of exposure is not clearly stated. Hence, information contained in Wright (90) and Martindale (56) is only summarised in this document and further reference to these two sources is not made. Unless otherwise stated information presented here is for the oral and parenteral routes. Toxicokinetic studies conducted with domestic and agricultural animals on specific veterinarian-related questions are not considered here.

6.1 Uptake

Absorption of penicillins occurs in the stomach and duodenum. For penicillins intended for oral administration, uptake varies from 30 to 90%. Peak levels in the serum are reached 1 to 2 hours after administration, but the presence of food may delay attainment of peak levels. Some penicillins are either poorly absorbed by the oral route e.g. ureidopenicillins, or broken down in the stomach by gastric juices, for example penicillin G. These latter two penicillins are routinely administered by parenteral routes to obtain pharmacologically sufficient systemic concentrations.

With the exception of one reference, (11), published studies on the toxicokinetics of penicillins following inhalation exposure have not be located. In that study, absorption of aerosolised benzylpenicillin with a mass median aerodynamic diameter of 2.81 ± 0.08 μm and a geometric standard deviation of 2.53 ± 0.05 μm was studied in the lungs of male Sprague-Dawley rats. Benzylpenicillin had an absorption half-time of 20.5 minutes (11). The authors showed that in general absorption of different drugs following inhaled aerosol administration was quite rapid, with absorption half-times ranging from less than 1 minute to more than 30

minutes. They also demonstrated that the water solubility and molecular weight influenced absorption. The low rate constant for absorption of benzylpenicillin reflects its low water solubility. However, it should be noted that the anatomy, morphology, and physiology of the respiratory systems of rodents and humans are very different (39).

In general, the bioavailability of penicillins will depend on their physical-chemical characteristics. Absorption of penicillins *via* the lungs may be affected by the water solubility, lipophilicity, molecular weight, physical state, and physical size (11, 39). For instance, the particle size and water solubility of a penicillin in the dust form will influence uptake in different regions of the respiratory system.

A fine dust would be expected to penetrate further into the lower airway system and more be absorbed there than for a coarser dust. Water-soluble penicillin dust is likely to be absorbed by the upper airway system. In addition, absorption *via* the gastronomical tract would also be expected to contribute to the total body burden as a portion of the inhaled dust may be swallowed after mucociliary clearance from the upper respiratory tract and/or nasal region. The fraction of dust orally absorbed is thought to be greater for water insoluble penicillins. Hence, the total body burden level of penicillin following inhalation of penicillin dusts is expected to be a contribution of pulmonary and oral absorption.

6.2. Distribution

Penicillin binding to serum proteins varies from 15% for aminopenicillins to 97% for dicloxacillins. Phenoxymethylpenicillin is 80% bound to protein. Approximately 95% of benzylpenicillin combines with protein through the β-lactam ring to form the benzylpenicilloyl (BPO) group, which is referred to as the "major" antigenic determinant (19-21, 91). Five per cent or less is referred to as the "minor" component which consist of benzylpenicillin itself and metabolised products including penicilloates, penilloates and possibly other products. The serum half-time is generally short, around 30 minutes for penicillin G and 60 minutes for extended-spectrum penicillins. All penicillins distribute well into most tissues except the prostate gland, eye, and cerebrospinal fluid. However, penicillins distribute into cerebrospinal fluid when the meninges are inflamed. In general, distribution depends on the molecular structure and protein binding of penicillins. The volume of distribution of penicillins is between 12 and 19 litres.

6.3 Biotransformation

Penicillins are either not or only minimally metabolised. For example, ureido-penicillins, which are mostly present in the serum in the free form are only metabolised by 10%. Other non-protein bound penicillins, benzylpenicillin, phenoxymethylpenicillin, ampicillin and amoxycillin are either not metabolised or metabolised to products including penicilloates, penilloates and possibly other

derivatives (19-21, 91). Phenoxymethylpenicillin is metabolised to a greater extent than benzylpenicillin in the liver.

6.4 Excretion

Of the systemically available penicillin and penicillin derived metabolites, most are readily and primarily excreted by the kidney through glomerular filtration and tubular secretion. Some penicillins are excreted (20-30%) by the biliary route e.g. cloxacillins, nafacillin, oxacillin, and the ureidopenicillins. Enterohepatic recycling of ampicillin may occur. Apparently the excretion in bile is dependent on the route of exposure. Renal failure will increase the systemic concentration of penicillins, especially those that are not excreted in the bile. Except for ureido-penicillins, other penicillins apparently exhibit linear dose-dependent clearance.

7. Mechanisms of toxicity

The adverse effects of concern are: i) bronchial hyperreactivity including asthma, ii) allergic contact dermatitis, and, iii) systemic urticaria probably including contact urticaria. Related effects including rhinitis, conjunctivitis and anaphylaxis have also been observed (40). Modified intestinal microflora, possibly caused by swallowed inhaled dust, has been reported from a single study (87).

7.1 Bronchial hyperreactivity including asthma

The following discussion is mainly based on the results detailed in this report and the publications of Chan-Yeung (13) and Cullinan and Newman Taylor (15).

For penicillin, symptoms both of the respiratory system and the vascular system observed in association with inhalation exposure are characteristic of Type I hypersensitivity. Classically Type I hypersensitivity is ascribed to being associated with an IgE-mediated mechanism (30), however, the involvement of IgE in the mechanism of penicillin-induced effects resulting from inhalation cannot be demonstrated. Therefore, based on the available evidence, penicillin-induced effects associated with inhalation exposure may be mediated by a non-IgE-mediated immunological mechanism. It is recognised that a non-immunological mechanism e.g. due to irritation to low levels of penicillin dust may be involved in situations where exposure to dust occurs. This mechanism may account for some specific symptoms, or co-contribute to other observed effects. However, it is difficult to discern the contribution of a non-immunological mechanism to the overall symptoms.

Although little is known about the details of the non-IgE-mediated immunological mechanism associated with penicillin-induced effects it is of interest to consider other substances that induce their effects by a non-IgE-mediated immunological mechanism. There are several examples of agents that cause asthma, for instance, isocyanates, plicatic acid, colophony, styrene, and

nickel and cobalt compounds. For isocyantes and plicatic acid pathological changes have been studied in detail in bronchial biopsies (13) Sloughing of epithelium, thickening of the basement membrane, and cellular infiltration particularly of eosinophiles occurs. Increased numbers of T-cells in bronchial mucosa, suggesting a role for T-cells, has been observed. It has also been suggested that B-cells may be involved. However, convincing evidences for the role of a cellular mediated mechanism are at present lacking (15). Alternatively pharmacological mediators have been suggested to be involved in the direct mediation of induced-effects for different substances (13, 15). These include, the direct action of complement, the direct release of histamine from peripheral leukocytes, release of substance P, β-adrenergic blocking action, and neural endopeptidase inhibition. Such actions may enhance an inflammatory response.

On the basis of the available information, it is not possible to determine the influence of predisposing factors (e.g. atopy, smoking) and cofactors (e.g. dust exposure, infection) on penicillin-induced respiratory effects.

7.2 Allergic contact dermatitis

The mechanism of delayed dermal hypersensitivity (Type IV allergy) for penicillin is based both on experiments with penicillin and on a general mechanism of action (41). The mechanism and reaction are considered to occur in two stages: sensitisation and elicitation.

Sensitisation produces a population of memory T-cells and takes about 10-14 days in humans. In brief, once penicillin is absorbed by the skin, the relatively low molecular weight hapten combines with protein to form a protein-hapten conjugate. This is internalised by epidermal Langerhans' cells, which subsequently leave the dermis and migrate as veiled cells, *via* efferent lymphatics, to the lymph nodes where processed hapten-protein conjugate complexes (in association with MHC class II molecules) are presented to $CD4^+$ lymphocytes, producing a population of memory $CD4^+$ T-cells. The subsequent elicitation phase involves recruitment of $CD4^+$ lymphocytes and monocytes. Re-exposure to the antigen results in binding to Langerhans' cells, which present the hapten-carrier complex to memory $CD4^+$ T-cells. These cells are activated to release IFN-γ, which activates keratinocytes to release proinflammatory cytokines. Degranulation and cytokine release by mast cells follows after contact with allergen. Macrophages invade the dermis and epidermis by 48 hours, resulting in allergic contact dermatitis.

7.3 Urticaria

Based on the available information it seems that systemically administered penicillin induces urticaria. However, contact urticaria may also be involved, as it is difficult to discern the type of exposure/absorption involved. Systemic urticaria may be associated with anaphylactic symptoms, such as wheezing, dysponea, syncope, abdominal pain, and vomiting. Immediate urticaria and angioedema are

associated with systemic exposure to all penicillins given as drugs to patients (90). Contact urticaria may be of immunological origin involving IgE-mediated hypersensitivity, or of non-immunological origin (40).

7.4 Cross-reactivity

Immunological cross-reactivity is high between penicillins and carbapems, cephalosporins and monobactams (64). Because the hypersensitivity is related to the basic penicillin structure, individuals who are allergic to benzylpenicillin must be assumed to be allergic to all penicillins; sensitised patients may also react to the cephalosporins and other β-lactam antibiotics (56). Cross-reactivity among synthetic and natural penicillins is due to their common 6-aminopenicillanic acid nucleus and sensitising groups (90).

7.5 Vulnerability

Penicillin-induced hypersensitivity is likely to have multi-factorial causation, involving individual susceptibility (genetic or acquired), penicillin exposure pattern (duration, intensity, frequency), physical-chemical properties of the penicillins, and physical state and health status of man (42, 91).

8. Effects in animals

8.1 Sensitisation

Published reports on animals, studying the effects of penicillin by inhalation exposure have not been located and only a few studies by the dermal route have been found.

Levine studied the dermal sensitivity potential of penicillin G on the shaved skin of male albino guinea pigs (52). The animals were sensitised with penicillin G by six percutaneous applications of 0.1 M solution of crystalline potassium penicillin G (KPG; 99% pure) or D-penicillamine·HCl, or D-benzylpenicillenic acid, or monosodium-D-α-benzylpenicilloate, or 2-benzyl-4-sodium hydroxy-methylene-(5)-oxazolone, or benzylpenilloaldehyde in a solvent composed of 95% ethanol, methylcellulose and Tween 80 (ECT; 45:45:10 v/v). A freshly prepared solution was used on each application of 0.05 ml spread onto a 2 cm circular area on the dorsal skin surface clipped free of hair. Applications to the same area of skin were made 3 times a week for 14 days. After 2 weeks the animals were patched tested for hypersensitivity with 0.1 M KPG in ECT solvent. Before elicitation the hair of the dorsal skin surface was carefully clipped. 24 hours later, 0.04 ml of the test substance was applied to the skin. It was not detailed if the applied test material was occluded for the exposure period. Reactions were recorded 48 hours later. As shown in Table 3, challenge with KPG and derivative gave a positive skin reaction.

Table 3. Percentage skin sensitisation in animals challenged with crystalline potassium penicillin G (52).

Sensitiser	No. animals reacting/total	Percentage sensitised
Potassium penicillin G	30/60	50
D-Penicillamine·HCl	36/41	88
D-Benzylpenicillenic acid	17/20	85
Monosodium-D-α-benzylpenicilloate	5/10	50
2-Benzyl-4-sodium hydroxymethylene-(5)-oxazolone	5/10	50
Benzylpenilloaldehyde	9/10	90

The skin-sensitising potential of penicillin G has also been studied in the guinea pig maximisation test, a predictive test recommended in the Organisation for Economic Co-operation and Development (OECD) test guideline 406 for skin sensitisation (69). In four studies (6, 31, 51, 55), penicillin G was classified as an extreme allergen (Grade V, 81-100% sensitised animals) and in one study (58), as a strong allergen (Grade IV, 65-80% sensitised animals) according to the Magnusson and Kligman classification (55). In the study by Kristofferson *et al*. cloxacillin and bacampicillin were also tested and both were classified as grade V allergens (51). For details, see Table 4. Extensive cross-reactivity was shown

Table 4. Guinea pig maximisation test conditions and results with penicillins.

Substance	Animal strain	Number (sex) of animals	Induction concentration	Challange concentration	Response % positive animals	Reference
Penicillin G	Hartly	20 (f)	3% id 5% pet ec	10% pet	100	(55)
Penicillin G	Pirbright	20 (10m,10f)	0.3% id, 5% pet ec	10% pet	74	(58)
Penicillin G	–[a]	27 (m)	0.63-2.5% id[b] 25% eth ec	5% eth	90[b]	(51)
Penicillin G	Dunkin-Hartly	20 (f)	25% eth id 25% eth ec	10% eth	90-100	(31)
Penicillin G	Dunkin-Hartly	20 (sex not specified)	1.0% id 10% ec	5.0% phys	100	(6)
Cloxacillin	–	16 (m)	0.32-1.25% id[b] 25% eth ec	5% eth	100[b]	(51)
Bacampicillin	–	26 (m)	0.16-0.63% id[b] 25% eth ec	5% eth	100[b]	(51)

Abbreviations: ec, epicutaneous; eth, ethanol; f, female; id, intradermal; m, male; pet, petrolatum; phys, 0.9% NaCl in H_2O.

[a] not given.

[b] Induction were performed, besides the ec treatment, with 3 different *id* concentrations. No difference in sensitisation rate could be detected and only the combined results were given.

between the penicillins in penicillin G and bacampicillin sensitised animals whereas the cloxacillin sensitised animals showed a more restricted reactivity (51).

The contact sensitising potential of penicillin G has also been tested in the local lymph node assay (6, 82). The method has been recommended in the OECD guideline 406 as a screening test for assessing skin sensitisation potential. In the case of a positive response a substance may be designated as a potential sensitiser and in the case of a negative result a guinea pig test must be conducted (69). The local lymph node assay utilises mice as the study animal and, in distinction to the guinea pig tests, it measures the response in the induction phase as cell proliferation ([3H]thymidine incorporation) in auricular lymph nodes after topical application of the test substance to the dorsum of the ears (43).

Penicillin G was dissolved in dimethylsulphoxide and tested in the local lymph node assay at three concentrations: 10, 25, and 50% (w/v). CBA/Ca mice were used. A stimulation index (SI) was calculated for each group, i.e. the test group proliferation value / control group (vehicle treated) proliferation value, and were 1.5, 3.8, and 8.9, for the three concentrations, respectively (6).

A chemical is classified as a potential sensitiser in the local lymph node assay if two criteria are fulfilled: i) At least one concentration of the test chemical induces a SI of a threefold or greater value than that of the vehicle control; ii) the result must not be incompatible with a biological dose-response (43). Penicillin G would thus be classified as a potential sensitiser according to the local lymph node assay.

It has been proposed (53) that the relative contact sensitising potential of a chemical can be ranked in the local lymph node assay by the EC_3-value (estimated concentration for SI = 3) obtained for that chemical. The EC_3-value for penicillin G calculated from Basketter and Scholes (6) is 20% (0.56 mol/dm^3(M)). EC_3-values for penicillin G has also been reported by Kimber *et al*. (44) in an inter-laboratory evaluation of the local lymph node assay, and were estimated to be 31.3, 16.1, 46.4, 46.5, and 41.1% for each of the five participating laboratories. These values are to be compared with EC_3-values of other allergens, e.g. 0.0765% (0.00383 M) for 2,4-dinitrochlorobenzene (5), 6.85-9.63% (0.317-0.445 M) for hexyl cinnamic aldehyde (33), and 5.8-14.5% (0.353-0.883 M) for eugenol (53). The first substance has a high sensitising potential whereas the two latter are considered to have a more moderate skin sensitising potential. Hence, based on this system penicillin would be ranked as even as a weaker sensitiser. However, the specificity of the local lymph node assay has been questioned and the assay requires further validation (2, 65).

In another method that utilises mice as the study animal and measures the cellularity in the popliteal lymph nodes, the mouse popliteal lymph node assay, penicillin G was tested in two inbred mouse strains (BALB/c and A/J) and one outbred strain (ICR) by four different laboratories (82). Two inbred mouse strains (BALB/c and A/J) and one outbred strain (ICR) were subcutaneously injected with saline solutions containing penicillin G (1.25, 2.5 and 5 mg/mouse) into one hind footpad and saline only was injected into the contralateral footpad. Popliteal

lymph node cellularity indices were determined on day 7. An approximate dose-dependent response was observed in all three strains. Popliteal lymph node responses in A/J, BALB/c and ICR mouse strains were high, intermediate and low, respectively. Dose-dependent popliteal lymph node responsiveness was almost comparable in four laboratories, although popliteal lymph node cellularity indices ranged from 1.5 to 3.2 for the moderate and maximum penicillin dose.

9. Observations in man

9.1 Occupational exposure

9.1.1 General

For convenience effects information is reported for different work categories separately. The studies detailed are cross-sectional or a series of case reports in the workplace. Analytical epidemiological studies have not been performed. Exposure levels are rarely reported, these studies are cited in this document.

Reports on factory workers concern exposure to penicillin dusts and mainly effects on the skin and respiratory system. One report details hypersensitivity pneumonitis in a single person. The information contained in this section is directly relevant for identifying a critical effect(s), dose-response (effect)-relationships, and relevant occupational exposure scenarios. These points are further discussed after this section.

9.1.2 Factory workers

In a non-peer reviewed report by Hanke and Patnode (32), they evaluated asthmatic symptoms in employees working with powdered and granulated penicillin. A combined industrial hygiene and medical-epidemiological evaluation of 36 penicillin workers (26 females and 10 males) and a comparison group (non-penicillin group) of 27 employees (23 females and 4 males) was conducted at a pharmaceutical company in USA. Personal breathing-zone environmental samples determined that the non-penicillin group had an average total dust exposure of 0.30 mg/m^3 (0.20-0.74 mg/m^3). Among workers exposed to penicillin, the following average levels of exposure were found for three penicillin subgroups: 5.97 mg/m^3 (range 2.48-12.47 mg/m^3; "high exposure") for production workers; 0.50 mg/m^3 (range 0.08-1.48 mg/m^3; "intermediate exposure") for packers in quality control; and, 0.29 mg/m^3 (range 0.12-0.45 mg/m^3; "low exposure") non-production workers. The penicillin group (combined subgroups) compared with the non-penicillin group was characterised by an excess prevalence of attacks of shortness of breath (15/36; 42% *cf*. 2/27; 7%). Increased prevalence of three additional asthma-like symptoms was demonstrated in females of the penicillin group: chronic cough (13/26; 50% *cf*. 2/23; 9%), wheezing (14/26; 54% *cf*. 2/23; 9%), and breathlessness (9/26; 35% *cf*. 1/23; 4%). No dose-response relationship was found between asthma-like symptoms and exposure of subgroups to penicillin dust. The authors could not conclude unequivocally that occupational asthma due

to penicillin dust did occur in the plant. They also proposed that the atopic status of a worker (presence of hay fever) was a predisposing factor for development of asthma.

Shmunes and co-workers studied 169 employees in a synthetic penicillin plant in a US National Institute for Occupational Safety and Health (NIOSH) study to correlate immunology reactions, allergic symptomatology and dustiness of the work area (83). Grouping of workers by range of dustiness in the workroom air was conducted. Air samples were collected on Millipore filters, Type AA, 0.8 μm pore size. The main groups were: Group A, 62 workers exposed to below 0.1 mg/m^3; B, 49 workers exposed to 0.1-9.9 mg/m^3; C, 42 workers exposed to 10-263 mg/m^3; and, D, 16 workers exposed episodically. A personal and/or family history of atopy was present in 49/169 workers. Only symptoms that appeared during employment were considered. Comparison of groups B and C separately with A showed statistically significant ($P = <0.01$) positive correlations among dust concentrations, allergic symptoms, and penicillin specific antibodies. Of 112 symptoms expressed by 67 workers, the most frequent target organs represented by the symptoms (greater than five elicitations) were the skin, upper respiratory tract, and eyes. Hemagglutinating anti-penicillin antibodies were detected in the sera of 73 employees. There was a statistically significant relationship between the presence or absence of antibodies (IgG and IgM) and the presence or absence of symptomology. Respiratory symptoms (wheezing) were found in 2% of those examined. The study indicates that employees exposed to ≥0.1 mg/m^3 penicillin can induce allergic symptoms.

In 1974, Davies *et al.*, reported on four workers in UK who developed respiratory complaints after working in an ampicillin production factory for up to 12 years (17). Three workers developed typical delayed-onset occupational asthma and rhinitis after 2 years of employment, while the fourth developed symptoms of cough and dyspnea suggesting occupational asthma. These patients were investigated by routine skin testing of ampicillin and related substances, as well as by bronchial and oral provocation studies. Skin tests were negative to ampicillin, benzylpenicillin, and 6-amino penicillanic acid. Three of the four patients had delayed and prolonged asthma and eosinophilia on inhalation challenge. All three patients reacted to commercial and purified ampicillin, while one reacted to purified 6-amino penicillanic acid and another to benzylpenicillin. The authors commented that this pattern of response indicated that impurities in the antibiotic preparations were unlikely to be the compounds responsible for the decline in forced expiratory volume in one second (FEV_1). Furthermore, oral antibiotic challenges confirmed systemic hyperresponsiveness in two of the three positive reactors.

A number of case reports with little information on exposure conditions are summarised in Table 5.

Table 5. Case reports concerning penicillin exposure of factory workers.

Exposure situation	No. of cases (sex)	Effects	Reference
Penicillin manufacturing for 12 year	1(f)	Hyper reactive airways, hypersensitivity pneumonitis. Authors conclusions: symptoms due to an immune reaction of cell-mediated type, hypersensitivity triggered by occupational exposure to penicillin.	(18)
Production of pivmecillinam and pivampicillin	45	All 45 had eczema mainly on the hands, arms, calves, and face. 19 also had hay fever (often of dual type) and/or asthma (often of delayed type). No signs of allergy of the eyes, nose, or lungs. All 45 were positive to at least one penicillin in patch test and 29 to more than one. All reactions could be seen on days 2 and 3. No delayed reactions were found.	(61)
Synthesis of pivmecillinam and pivampicillin	14	Frequent reports of rhinitis, eczema, and urticaria among 6 workers involved in penicillin synthesis. Frequent reports of rhinitis and concjunctivitis among 8 workers involved in powder feeding of penicillin and flavour additives, symptoms worsened when penicillin exposure increased. Basophil histamine release positive in 5/14 and patch test positive in 4/14. Author's conclusion: immediate and delayed immune responses due to airborne exposures to penicillin.	(63)
Penicillin manufacturing	17	Positive response to penicillins in patch test remained after 14 year.	(60)
Production of pivmecillinam and pivampicillin	45	All 45 had contact dermatitis on face and hands. 27 reacted to pivampicillin and 33 to pivmecillinam. 18/27 reacted to both ampicillin and pivampicillin. Only 4/33 reacted to both mecillinam and pivmecillinam, probably due to the low solubility of mecillinam. Only few reacted to penicillins G and V.	(64)
Production of pivampicillin	56	56 workers with allergy over 15 year. Significant decrease in number of patients with allergy after improvement of the work environment resulting in decreased levels of airborne antibiotics.	(62)
Production of penicillins	86	86 allergic cases of 331 workers examined, where of 79 contact eczema, 6 urticaria and 1 bronchial asthma. Most had never been treated with penicillin. Positive skin reactions to penicillin G were found only among workers employed in the "dusty departments", but with no relation to length of employment.	(74)

Table 5. Cont.

Exposure situation	No. of cases (sex)	Effects	Reference
Filling ampoules with penicillin and ampicillin	1(f)	Dermatitis on hands and forearms. Tested negative to natural penicillins but positive to semisynthetic penicillins.	(76)
Production of penicillins	14	14 workers of 34 examined determined to have occupationally related contact dermatitis. 8/14 positive to penicillin G in patch test.	(80)
Production of penicillins	58	58 workers of 100 examined determined to have occupationally related contact dermatitis. 8/58 positive to penicillin G in patch test.	(71)
Production of penicillins	8	8 workers of 31 examined diagnosed to have contact allergy to penicillin.	(80)
Production of bacampicillin	9(m)	Symptoms of hypersensitivity. 8/9 positive to bacampicillin in patch test. Two of these workers also had rhinitis and conjunctivitis. Of all penicillins manufactured by the company, bacampicillin was the major occupational sensitiser.	(84, 85)
Production of penicillins	8	Various hypersensitivity symptoms in connection with work.	(84)
Production of penicillins	–	Penicillin workers more often showed intestinal floral modification (92%) than those working with streptomycin (81%) and tetracycline (76%). Total number of examined workers was 441.	(87) cited in (83)
Manufacture of semisynthetic penicillins	–	Workers developed attacks of shortness of breath and wheezing. Inhalation challenge testing with penicillin V-lactose produced asthmatic reactions.	(7)
Production of penicillins	9	9 workers of 135 examined demonstrated sensitisation of the respiratory airways to penicillin.	(12)
Production of penicillins	7	7 workers of 167 examined showed positive reaction to penicillin specific antibodies.	(28)
Production of antibiotics	31	31 workers of 500 examined positive to penicillin in patch test.	(46)

Table 5. Cont.

Exposure situation	No. of cases (sex)	Effects	Reference
Manufacture of penicillin	3	Coryza, sneezing, lacrimation, headache, coughing, wheezing, skin itching, redness, and swelling, especially of the eyelids and the skin under the eyes. Signs of upper respiratory allergy similar to pollinosis and other conditions of hypersensitivity, signs of bronchial asthma, and dry, scaly and erythematous skin in 2 workers. Skin scratch test with penicillin caused erythema. One worker given sick leave was completely asymptomatic after two weeks.	(72)
Manufacture of penicillin	28	28 of 289 packers developed contact dermatitis and black hairy tongue.	Suskind *et al*. 1953 cited in (83)
Pharmaceutical plant	28	28 of 43 positive patch test reactions were due to penicillin in penicillin workers.	(16)
Manufacture of penicillin	4	Dermatitis due to exposure to sodium and potassium penicillin salts. Workers more sensitive to pure crystalline penicillin than to any particular impurity in the commercial product. 2/4 had a strong reaction to intradermal sodium penicillin G, 1 had a slight reaction, and 1 had no reaction.	(29)

9.1.3 Health-care-personnel (medical workers), veterinarians, and laboratory workers

Case reports on health-care personnel, veterinarians, and laboratory workers with little or no information on exposure are summarised in Table 6.

9.1.4 Patients

Data on patients is briefly reviewed in this document as the results are relevant for dermal and inhalation exposure to penicillin.

According to Martindale the most common adverse effects of penicillins used by patients are hypersensitivity reactions, especially skin rashes and occasionally anaphylaxis, which has sometimes been fatal (56).

In a comprehensive review written by DeSwarte, it is reported that bronchial asthma has been shown in patients treated with aerosolised penicillin (19). Also contact dermatitis (Type IV reaction) due to the sensitising properties of topically applied penicillin has been demonstrated in patients (see also Friedlaender *et al.* (29). These treatments by the inhalation and dermal routes have been discontinued. According to DeSwarte, anaphylactic and urticarial reactions, typical of Type I reactions, have been documented to be caused by topical application. The review does not, however, cite the source of this information. Fisher also refers to aerosol and topically applied penicillin as inducing allergy without citing the source (24).

9.2 Experimental exposure

The contact sensitising potential of penicillin G has been experimentally estimated in humans in the human maximisation test (48) and the "reduced maximisation test" (47). The results are summarised in Table 7.

A panel of 24 healthy male prisoners, aged 18-50 years (90% of the subjects were black) were used as experimental subjects. For induction exposure a 3.8 x 3.8 cm patch containing 1.0 ml of 25% (w/w) penicillin G in petrolatum were applied for 48 hours on the forearm or calf under occlusion for 48 hours. The induction site was pre-treated with sodium lauryl sulphate for 24 hours to induce a moderate inflammatory reaction. This sequence of alternating 24 hours irritant and 48 hours penicillin patches were repeated for a total of five exposures of each (48). The rest period between induction and challenge was not stated but was probably two weeks (49). For challenge, an occlusive patch (2.5 x 2.5 cm) containing 0.4 ml of 10% (w/w) penicillin in petrolatum were applied to the lower back for 48 hours, after pre-treatment of the test site for one hour with sodium laruyl sulphate. The challenge reaction was read immediately after removal of the patch and again in another two days. An evident erythema, clearly more inflammatory than a control patch consisting of petrolatum, was the minimum requirement to be considered as a positive response. A sensitisation rate of 16/24 (67%) was found, which classifies penicillin G as a strong (Grade IV, 56-80% sensitisation rate) sensitiser in this test (48). The experiment was repeated on three

Table 6. Case reports concerning penicillin exposure in health care workers, veterinarians, and laboratory workers.

Study group / exposure condition	No. of cases (sex)	Effects	Reference
Nurses	21	21 of 333 nurses were positive to penicillin in a patch test. Cross-reactivity to ampicillin (14/21), carbenicillin (2/21), and cloxacillin (1/21) was also found.	(78)
Nurse administering penicillin injections	6	Anaphylactic shock only in 3, anaphylactic shock + urticaria in 1, urticaria + rhinitis in 1, urticaria only in 1. No exposure details given. Severity and duration of urticaria not described.	(75)
Nurses	12	Contact allergy to penicillin diagnosed in 12/26 nurses.	(77)
Physicians	2	Contact allergy to penicillin diagnosed in 2/17 physicians.	(77)
Nurses with contact dermatitis	19	29 of 65 nurses determined to have occupational contact dermatitis. 19 of 29 positive to penicillin G by patch test.	(80)
Nurses with contact dermatitis	3	2 of 24 nurses diagnosed as having occupational contact dermatitis were positive to ampicillin and 1 of 24 to penicillum by patch test.	(73)
Nurse	1(f)	Erythema and intense swelling of the face, with severe pruritus some hours after a solution of benzylpenicillin spurted onto the face when giving an injection.	(70)
Nurse administering penicillin injections	1(f)	In 1953, aged 20, the nurse developed urticaria 15 to 30 minutes after an intramuscular injection of penicillin. Subsequent occupational exposure to penicillin or cephalosporine solutions regularly induced pruritus and occupational urticarial lesions. In 1964 she developed urticaria, hypotension, wheezing, and gastrointestinal distress 20-30 minutes after ingestion of milk and cereal. In 1974, she developed urticaria, bronchospasm, gastrointestinal distress, and hypotension when exposed to nafcillin. In 1980, shortly after eating cheese and croutons made from stale bread, she developed acute anaphylaxis. She was therefore considered to be exquisitely sensitive to penicillin. Subsequently she underwent a successful desensitisation treatment.	(66)

Table 6. Cont.

Study group / exposure condition	No. of cases (sex)	Effects	Reference
Health care workers	24	In 24 of 61 cases of drug-induced occupational eczema a contact allergy to ampicillin and 2/61 to penicillin G was confirmed by patch test. The intradermal test with ampicillin was positive in 12 of 21. The author proposed that the relationship between the chemical structure and the sensitising properties support the hypothesis that the free amino group of the side chain seems to play a role for the sensitising capacity of ampicillin.	(81)
Nurse administering penicillin injections	1(f)	Swelling of eyelids and face. Patch test negative, but intradermal tests produced redness, swelling and near complete closure of the eyes on the following day.	(68)
Veterinary surgeons	6	All 6 strongly positive to penethamate, but only 3 to benzylpenicillin Dermatitis was provoked or aggravated when using penethamate hydriodide for local treatment of mastitis in cows. Penethamate is a base and benzylpenicillin is an acid. The author suggests that penethamate possibly owes both its therapeutic and its strongly sensitising properties to its ease to penetrate biological membranes.	(34)
Veterinary surgeons	6	6 of 9 were sensitive to penicillin or its derivatives, e.g. penethamate hydroiodide.	(36)
Veterinary surgeons	37	In 36 veterinary surgeons with incapacitating allergic contact dermatitis, 5 reactions to procain were associated with a positive patch test to procain-penicillin.	(35)
Veterinarians	4	3 of 34 Norwegian veterinarians were positive to procaine and/or benzathine penicillin and 1/34 to all three antigens tested (benzyl-, procaine or benzathine penicillin).	(23)
Veterinarians with dermatitis	2	2 of 26 veterinarians diagnosed with dermatitis were positive to penicillin G in a patch test.	(79)
Veterinarians	9	9 of 31 were determined to have occupational contact dermatitis and 3 of 9 were positive to penicillin G in a patch test.	(80)
Laboratory workers handling bacampicillin	2(f)	2 of 2 with eczema on the hands gave positive patch tests to bacampicillin.	(85)

Table 7. Summary of human maximisation test and "reduced maximisation test" results with penicillin G (47, 48). For description of the methods see the text.

	Induction		Sensitisation rate	
Experiment No.	Concentration (%, w/w)	No. of patches (exposures)	Positive reactions/ No. subjects	%
1	25	5	16/24	67
2	25	5	16/23	70
3	25	5	12/23	52
4	25	5	13/25	52
5	0.2	5	2/22	9
	1.0	5	4/22	18
	5.0	5	7/25	28
	10	5	11/25	44
	25	5	16/25	64
6	10	3	1/25	4
	10	5	5/25	20
	10	10	10/21	48
	10	15	16/21	76
7[a]	0.1	1 x 5	0/23	0
	0.1	2 x 5	2/22	9
	0.1	3 x 5	6/24	25
8	0.1	15	–[b]	–

[a] Induction was conducted with one to three sensitisation courses, each consisting of five exposures. The time period between courses was not given.
[b] not given.

occasions and sensitisation rates of 16/23 (70%), 12/23 (52%), and 13/25 (52%) were obtained, respectively. The two latter results with penicillin G are classifiable as a moderate sensitiser (Grade III, 32-52% sensitisation rate). The author concludes that the classification of penicillin G as a strong contact sensitiser corresponds well with clinical experience and that sensitisation rating may have been higher if only Caucasian subjects had been tested (48).

In an additional report, a modified human maximisation test, "reduced maximisation test", was used (47). The testing procedure was exactly the same as described above except that different concentrations, non-maximal, were used for induction. Induction exposures to 0.2, 1.0, 5.0, 10, and 25% (w/w) penicillin G in petrolatum sensitised 9% (2/22), 18% (4/22), 28% (7/25), 44% (11/25), and 76% (16/21) of the tested subjects, respectively (47).

The influence of the number of exposures during the induction procedure on sensitisation rate was also investigated (47). The same site on one extremity was exposed for a maximum of five per site; each course of five exposures was conducted on a new fixed site on the same extremity. A 10% concentration of penicillin G was used as induction concentration and 3, 5, 10, and 15 exposures

sensitised 4% (1/25), 20% (5/25), 48% (10/21), and 64% (16/25) of the tested subjects, respectively (47).

Sensitisation rates with threshold induction concentrations of penicillin G, 0.1%, were tested with three sensitisation courses, each consisting of five exposures (47). Each course was applied to the same site on one extremity; a new site was used for each five exposure courses (the time interval between courses were not given). One, two, and three sensitisation course sensitised 0 (0/23), 9 (2/22), and 25% (6/25), respectively. In the same article the author states (47) that they have not succeeded in producing sensitisation with 15 exposures to 0.1% penicillin G (see Table 7, experiment 7 and 8). The difference in these two experiments is not clear except that in experiment 7 each course of five induction exposures seems to be more clustered.

10. Dose-effect and dose-response relationship

Based on the available information it is difficult to establish a dose-effect relationship.

Shmunes *et al*. reported a significantly higher incidence of allergic symptoms in workers exposed to 0.1-9.9 mg/m^3 as compared to below 0.1 mg/m^3 (83).

In a non-peer reviewed study conducted by Hanke & Patnode (32), the excessive prevalence of asthma-like respiratory symptoms was observed in penicillin-exposed workers to a total dust concentration of 0.29 mg/m^3 (0.12-0.45 mg/m^3). However, a dose-response relationship was not demonstrated between asthma-like symptoms and exposure to penicillin dust.

In both theses studies the effects have been correlated with the total dust level, assuming that all dust emanated from penicillin. Such an assumption may be valid in some cases, principally when the only dust source is dry penicillins or dry drug formulations with known penicillin content. However, in most other cases such an assumption would lead to a significant error in the determination of the airborne penicillin concentrations and does, therefore, not represent an adequate approach.

A semi-quantitative relationship between the inhibition of penicillin-sensitive bacteria, and respiratory and dermal symptoms has been demonstrated (62); however, this information is difficult to use in an exposure-response analysis unless the degree of inhibition of bacterial growth is standardised.

Qualitative descriptions of dustiness and association with effects of penicillin cannot be used in this document (74).

11. Previous evaluations by (inter)national bodies

The International Agency for Research on Cancer (IARC) conducted an evaluation of carcinogenic risks to humans of ampicillin (trihydrate and sodium salt) considering oral and parenteral routes of administration (38). The overall

evaluation was that "Ampicillin *is not classifiable as to its carcinogenicity to humans (Group 3)*".

European Centre for Ecotoxicology and Toxicology for Chemicals (ECETOC), stated that penicillin G [calcium and potassium salts CAS No. 973-53-5 and 113-98-4] are considered as human and animal skin sensitisers (22).

12. Evaluation of human health risks

12.1 Assessment of health risks

For workers, there is evidence that exposure in their working environment can cause asthma. Several authors have described cases of workers employed in the manufacture of synthetic penicillin antibiotics developing attacks of shortness of breath and wheezing (e.g. (32)).

In addition, penicillin aerosols have been withdrawn for the treatment of patients because of their sensitising properties.

There is convincing evidence that penicillin causes delayed skin hypersensitivity due to exposure to both penicillin dusts and solutions. This has been shown in the majority of the occupationally related reports detailed in chapter 9 "Observations in Man".

Urticaria has been observed in several studies. The available information both on occupational and non-occupational exposure routes show that systemic-dependent urticaria and probably contact-dependent urticaria are critical effects.

Hoyos *et al*. described the unusual co-existence of hypersensitivity pneumonitis (18). Penicillin-induced hypersensitivity pneumonitis has been rarely described and the authors comment that the cause-effect association has never been established to their knowledge (89). Hence, this effect cannot at present be regarded as representative.

Concerning the single report on modified human intestinal microflora (87), this would probably occur due to oral exposure of swallowed inhaled dust. Because this study is poorly reported and it does not seem to be representative, this study cannot be considered to be of adequate quality to justify this as an adverse effect.

Thus, it is concluded that three adverse effects are convincingly substantiated to be health risks for workers occupationally exposed to penicillin dusts and solutions:

- bronchial hypersensitivity including asthma by a non-IgE-dependent mechanism.
- allergic contact dermatitis (Type IV).
- systemic urticaria probably including contact urticaria.

12.2 Groups at extra risk

Because immunological cross-reactivity is high between penicillins and carbapems, cephalosporins and monobactams (64), workers that exhibit cross-reactivity should be regarded as a group at extra risk.

Based on available data, it is not possible to determine whether atopic individuals in general are more sensitive to the adverse effects of penicillin.

12.3 Scientific basis for an occupational exposure limit

The critical adverse effect considered for the basis of an occupational exposure limit is the development of occupational asthma as reported in the non-peer reviewed report by Hanke and Patnode (32). In this study, an excessive prevalence of asthma-like symptoms was observed in penicillin-exposed workers with a total dust exposure of 0.29 mg/m^3 (0.12-0.45 mg/m^3).

13. Research needs

The following information is required to improve this risk assessment of penicillin on human health and support risk management considerations.

- Development of robust and simple sampling and analytical methods for airborne penicillins in workplace air.
- Collection of exposure information both environmental and biological (effect) monitoring data and/or better characterise work activities that may result in exposure to penicillin for different occupational groups. It is recognised that monitoring and industrial field survey information may be available to regulatory authorities and it is therefore encouraged that this information be collated and published.
- Characterise the mechanism of penicillin-induced non-IgE-mediated respiratory hypersensitivity/-reactivity.
- Development of a reliable and convenient test system to determine the potential for respiratory and dermal hypersensitivity. This is considered especially relevant for penicillin-induced non-IgE-dependent respiratory hyperreactivity. This test may then be used as a biological effect monitoring test for surveillance in the occupational setting.
- Need to conduct a longitudinal epidemiological study to determine the association between exposure to penicillin and the incidence and prevalence of dermal and respiratory effects.

14. Summary

Moore GA, Nygren O. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 134. Penicillins.* Arbete och Hälsa 2004;6:1-57.

This document reviews the health risks from occupational exposure to penicillins. Penicillins are produced in large amounts for use as antibiotics. Few quantitative data on occupational exposure are available, however, the potential exposure to penicillins is identified among several worker groups.

The adverse health effects associated with inhalatory and dermal exposure to penicillins are:
– bronchial hypersensitivity including asthma
– allergic contact dermatitis and,
– systemic urticaria probably including contact urticaria.

In a non peer-reviewed report, workers in the penicillin manufacturing industry exposed to a total dust concentration of 0.29 mg/m^3 (0.12-0.45 mg/m^3) had an excess prevalence of asthma-like symptoms.

Keywords: allergy, exposure levels, health effects, occupational exposure limit, penicillin, review, risk assessment, sensitisation.

15. Summary in Swedish

Moore GA, Nygren O. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 134. Penicillins.* Arbete och Hälsa 2004;6:1-57.

Detta dokument behandlar hälsorisker vid yrkesmässig exponering för penicilliner. Penicilliner produceras i stora kvantiteter för användning som antibiotika. Få kvantitativa uppgifter om exponeringsnivåer föreligger men flera yrkeskategorier med möjlig exponering är identifierade.

De kritiska effekter associerade med inhalation och hudexponering för penicilliner är:
– bronkiell hypersensibilisering och astma,
– allergiskt kontakteksem,
– systemisk urtikaria troligen inkluderande kontakturtikaria.

I en rapport (ej publicerad i en peer-review-granskad tidskrift) uppvisade arbetare inom penicillin tillverkningsindustrin exponerade för en total dammhalt på 0.29 mg/m^3 (0.12-0.45 mg/m^3) en ökad förekomst av astma-liknande symptom.

Nyckelord: allergi, exponeringsnivåer, hygieniska gränsvärden, hälsoeffekter, penicillin, riskbedömning, sensibilisering, översikt

16. References

1. Agius R. Occupational exposure limits for therapeutic substances. *Ann Occup Hyg* 1989;33:555-562.
2. Andersen KE. Methods for animal studies on detection and assessment of chemical skin allergens. In: Flyvholm MA, Andersen KE, Baranski B, Sarlo K, eds. *Criteria for classification of skin- and airway-sensitizing substances in the work and general environment*. Copenhagen: World Health Organization, Regional Office for Europe, 1997:78-83.
3. Apoteket. *Svensk läkemedelsstatistik*. Stockholm: Apoteket AB, 1999.
4. Apoteksbolaget. *Läkemedelsboken 1989/1990*. Stockholm: Apoteksbolaget AB, 1990: 305-307.
5. Basketter DA, Dearman RJ, Hilton J, Kimber I. Dinitrohalobenzenes: evaluation of relative skin sensitization potential using the local lymph node assay. *Contact Dermatitis* 1997;36:97-100.
6. Basketter DA, Scholes EW. Comparison of the local lymph node assay with the guinea-pig maximization test for the detection of a range of contact allergens. *Food Chem Toxicol* 1992;30:65-69.
7. Baur X, Fruhmann G. Berufsbedingtes asthma bronchiale allergischer und irritativer genese [Bronchial asthma of allergic or irritative origin as an occupational disease (author's transl)]. *Prax Klin Pneumol* 1979;33 Suppl 1:317-322.
8. Bellgardt KJ. Process models for production of beta-lactam antibiotics. *Adv Biochem Eng Biotechnol* 1998;60:153-194.
9. Bjornerot L, Franklin A, Tysen E. Usage of antibacterial and antiparasitic drugs in animals in Sweden between 1988 and 1993. *Vet Rec* 1996;139:282-286.
10. Boison JO. Chromatographic methods of analysis for penicillins in food-animal tissues and their significance in regulatory programs for residue reduction and avoidance. *J Chromatogr* 1992;624:171-194.
11. Brown RA, Jr., Schanker LS. Absorption of aerosolized drugs from the rat lung. *Drug Metab Dispos* 1983;11:355-360.
12. Brusilovskii ES, Tereshchenko Iu A, Sarova MA. Specific diagnosis of allergic diseases of the aeriferous pathways in persons involved in the production of antibiotics. (Article in Russian). *Sov Med* 1970;33:33-36.
13. Chan-Yeung M. Occupational asthma. *Environ Health Perspect* 1995;103 Suppl 6:249-252.
14. Corey SV, Taylor GC. Penicillins, cephalosporins, quinolones. *Clin Podiatr Med Surg* 1992;9:385-407.
15. Cullinan P, Newman Taylor AJ. Occupational Asthma. In: Kay AB, ed. *Allergy and allergic disease*. Oxford: Blackwell Science, 1997.
16. Dalton JE, Pierce JD. Dermatological problems among pharmaceutical workers. *AMA Arch Derm and Syph* 1951;64:667.
17. Davies RJ, Hendrick DJ, Pepys J. Asthma due to inhaled chemical agents: ampicillin, benzyl penicillin, 6 amino penicillanic acid and related substances. *Clin Allergy* 1974;4:227-247.
18. de Hoyos A, Holness DL, Tarlo SM. Hypersensitivity pneumonitis and airways hyperreactivity induced by occupational exposure to penicillin. *Chest* 1993;103:303-304.
19. DeSwarte RD. Drug allergy. In: Patterson R, ed. *Allergic Diseases, Diagnosis and Management*. 3rd ed. Philadelphia: Lippincott, 1985:505-661.
20. Dewdney JM. Immunology of the antibiotics. In: Sela M, ed. *The Antigens*. New York: Academic Press, 1977:73-245.
21. DeWeck AL. Penicillins and cephalosporins. In: DeWeck AL, Bundgaard H, eds. *Allergic reactions to drugs*. Berlin: Springer-Verlag, 1983:423-482. 1983.

22. ECETOC. *Skin and respiratory sensitisers: Reference chemicals data bank*. Technical report no. 77. Brussels: European Centre for Ecotoxicology and Toxicology for Chemicals, 1999:73.

23. Falk ES, Hektoen H, Thune PO. Skin and respiratory tract symptoms in veterinary surgeons. *Contact Dermatitis* 1985;12:274-278.

24. Fisher AA. Allergic contact dermatitis to penicillin and streptomycin. *Cutis* 1983;32:314, 318, 324.

25. Fleming A. Classics in infectious diseases: on the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae by Alexander Fleming. Reprinted from the British Journal of Experimental Pathology 10:226-236, 1929. *Rev Infect Dis* 1980;2:129-139.

26. Flink O, Hamilton L, Frändén G. Penicillinkontamination på apotek. *Sven Farm Tidskr* 1980;84:144-148.

27. Florey K, ed. *Analytical profiles of drug substances*. Vol 1-14. New York: Academic Press, 1971-1985.

28. Foà B, Cavagna G, Lacati G, Terzaghi E. Applicazione della penicilloil-polilisina nello studio della sensibilizzazione alla penicillina in operai di una fabrica di antibiotici. [The use of penicilloyl-polylysine in the study of penicillin sensitization among workers of an antibiotic factory]. *Med Lav* 1966;57:175-183.

29. Friedlander AS, Watrous RM, Feinberg SM. Contact dermatitis from penicillin. *Arch Derm Syph (Chicago)* 1946;54:517-523.

30. Gell PG, Coombs RR, eds. *Clinical aspects of immunology*. Oxford: Blackwell Scientific Publications, 1963.

31. Guillot JP, Gonnet JF, Clement C, Faccini JM. Comparative study of methods chosen by the Association Francaise de Normalisation (AFNOR) for evaluating sensitizing potential in the albino guinea-pig. *Food Chem Toxicol* 1983;21:795-805.

32. Hanke W, Patnode R. *Health hazard evaluation report no. GHE 80-169-1300*. Mylan Pharmaceutical, Morgantown, West Virginia. Cincinnati, OH: National Institute for Occupational Safety and Health, 1983.

33. Hilton J, Dearmann RJ, Harvey P, Evans P, Basketter DA, Kimber I. Temporal stability of hexyl cinnamic aldehyde in the local lymph node assay. *The Toxicologist* 1998;42:173 (Abstract).

34. Hjorth N. Occupational dermatitis among veterinary surgeons caused by penethamate (benzyl penicillin-beta-diethylaminoethylester). *Berufsdermatosen* 1967;15:163-175.

35. Hjorth N, Roed-Petersen J. Allergic contact dermatitis in veterinary surgeons. *Contact Dermatitis* 1980;6:27-29.

36. Hjorth N, Weismann K. Occupational dermatitis among veterinary surgeons caused by spiramycin, tylosin, and penethamate. *Acta Derm Venereol* 1973;53:229-232.

37. Hou JP, Poole JW. Beta-lactam antibiotics: their physicochemical properties and biological activities in relation to structure. *J Pharm Sci* 1971;60:503-532.

38. IARC. Pharmaceutical drugs. In: *IARC Monographs on the evaluation of carcinogenic risks to humans*. Vol 50. Lyon, France: International Agency for Research on Cancer, 1990:153-167.

39. IPCS. International Programme on Chemical Safety (IPCS). Respiratory toxicology and risk assessment. *Proceedings of an International Symposium*. IPCS Joint Series 18. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1994.

40. IPCS. *Principles and methods for assessing allergic hypersensitisation associated with exposure to chemicals*. Environmental Health Criteria 212. Geneva: International Programme on Chemical Safety, World Health Organisation, 1999:88-123.

41. Kimber I. Chemical-induced hypersensitivity. In: Smialowicz RJ, Holsapple MP, eds. *Experimental Immunotoxicology*. Boca Raton, FL: CRC Press, 1996:391-417.

42. Kimber I. Biomarkers of immunotoxicity in man. *Hum Exp Toxicol* 1995;14:148-149.
43. Kimber I, Basketter DA. The murine local lymph node assay: a commentary on collaborative studies and new directions. *Food Chem Toxicol* 1992;30:165-169.
44. Kimber I, Hilton J, Dearman RJ, Gerberick GF, Ryan CA, Basketter DA, Lea L, House RV, Ladics GS, Loveless SE, Hastings KL. Assessment of the skin sensitization potential of topical medicaments using the local lymph node assay: an interlaboratory evaluation. *J Toxicol Environ Health A* 1998;53:563-579.
45. Kirk RE, Othmer DF, Grayson M. *Kirk-Othmer Concise encyclopedia of chemical technology*. New York: Wiley cop., 1985.
46. Kleine-Natrop HE. Antibiotika als berufliche allergene in der arzneimittelindustrie. *Berufsdermatosen* 1956;4:269.
47. Kligman AM. The identification of contact allergens by human assay. II. Factors influencing the induction and measurement of allergic contact dermatitis. *J Invest Dermatol* 1966;47:375-392.
48. Kligman AM. The identification of contact allergens by human assay. III. The maximization test: a procedure for screening and rating contact sensitizers. *J Invest Dermatol* 1966;47:393-409.
49. Kligman AM. The SLS provocative patch test in allergic contact sensitization. *J Invest Dermatol* 1966;46:573-583.
50. Kobayashi S. Occupational asthma due to inhalation of pharmaceutical dusts and other chemical agents. In: Yamamura Y, Frick OL, Horiuchi Y, eds. *Allergology: proceedings of the VIII International Congress of Allergology*, Tokyo 14-20 October, 1973. New York: American Elisevier Publishing, 1974:124-132.
51. Kristofferson A, Ahlstedt S, Enander I. Contact sensitivity in guinea pigs to different penicillins. *Int Arch Allergy Appl Immunol* 1982;69:316-321.
52. Levine BB. Studies on the mechanism of the formation of the penicillin antigen. I. Delayed allergic cross-reactions among penicillin G and its degradation products. *J Exp Med* 1960;112:1131-1156.
53. Loveless SE, Ladics GS, Gerberick GF, Ryan CA, Basketter DA, Scholes EW, House RV, Hilton J, Dearman RJ, Kimber I. Further evaluation of the local lymph node assay in the final phase of an international collaborative trial. *Toxicology* 1996;108:141-152.
54. Läkemedelsinformation AB (LINFO). *FASS 2000 - Läkemedel i Sverige* [Pharmaceutical products in Sweden]. Pp39; Antimox®:Pp150; Amoxicillin Scand Pharma:Pp154-160; Diclocil:Pp414-415; Heracillin®:Pp647; Imacillin®:Pp677-678; Kåvepenin®:771-772; Pondocillin®:Pp1073-1074, Selexid®:1193-1194. Oslo: Elanders Publishing AS, 2000.
55. Magnusson B, Kligman AM. The identification of contact allergens by animal assay. The guinea pig maximization test. *J Invest Dermatol* 1969;52:268-276.
56. Martindale W. *Martindale - The extra pharmacopoeia*. 30th ed. In: Reynolds JEF, ed. London: Pharmaceutical Press, 1993.
57. Mathews KP. Clinical spectrum of allergic and pseudoallergic drug reactions. *J Allergy Clin Immunol* 1984;74:558-566.
58. Maurer T, Thomann P, Weirich EG, Hess R. Predictive evaluation in animals of the contact allergenic potential of medically important substances. II. Comparison of different methods of cutaneous sensitization with "weak" allergens. *Contact Dermatitis* 1979;5:1-10.
59. Miners JO. The analysis of penicillins in biological fluids and pharmaceutical preparations by high-performance liquid chromatography: A review. *J Liq Chromatogr* 1985;8:2827-2843.
60. Moller NE, Jeppesen K. Patch testing with semisynthetic penicillins. *Contact Dermatitis* 1987;16:227-228.
61. Moller NE, Nielsen B, von Wurden K. Contact dermatitis to semisynthetic penicillins in factory workers. *Contact Dermatitis* 1986;14:307-311.

62. Moller NE, Nielsen B, von Wurden K. Changes in penicillin contamination and allergy in factory workers. *Contact Dermatitis* 1990;22:106-107.
63. Moller NE, Skov PS, Norn S. Allergic and pseudo-allergic reactions caused by penicillins, cocoa and peppermint additives in penicillin factory workers examined by basophil histamine release. *Acta Pharmacol Toxicol (Copenh)* 1984;55:139-144.
64. Moller NE, von Wurden K. Hypersensitivity to semisynthetic penicillins and cross-reactivity with penicillin. *Contact Dermatitis* 1992;26:351-352.
65. Montelius J, Wahlkvist H, Boman A, Fernstrom P, Grabergs L, Wahlberg JE. Experience with the murine local lymph node assay: inability to discriminate between allergens and irritants. *Acta Derm Venereol* 1994;74:22-27.
66. Naclerio R, Mizrahi EA, Adkinson NF, Jr. Immunologic observations during desensitization and maintenance of clinical tolerance to penicillin. *J Allergy Clin Immunol* 1983;71:294-301.
67. Naumann BD, Sargent EV. Setting occupational exposure limits for pharmaceuticals. *Occup Med* 1997;12:67-80.
68. O'Driscoll BJ. Desensitization of nurses allergic to penicillin. *Br Med J* 1955;2:473-475.
69. OECD. *Guideline for testing of chemicals No. 406 - Skin Sensitization*. Paris: Organisation for Economic Co-operation and Development, 1993.
70. Pecegueiro M. Occupational contact dermatitis from penicillin. *Contact Dermatitis* 1990;23:190-191.
71. Rembadel P, Rudzki E. Occupational allergy in the production of drugs (Article in Polish). *Pol Tyg Lek* 1990;45:82-84.
72. Roberts AE. Occupational allergic reactions among workers in a penicillin manufacturing plant; simple and inexpensive method of diagnosis and treatment. *A M A Arch Ind Hyg Occup Med* 1953;8:340-346.
73. Rudzki E. Occupational dermatitis among health service workers. *Derm Beruf Umwelt* 1979;27:112-115.
74. Rudzki E, Lukasiak B, Leszczy'Nski W. Penicillin Hypersensitivity and Haemagglutinating Antibodies in Workers at a Penicillin Factory. *Acta Allergol* 1965;20:206-214.
75. Rudzki E, Rebandel P. Occupational contact urticaria from penicillin. *Contact Dermatitis* 1985;13:192.
76. Rudzki E, Rebandel P. Hypersensitivity to semisynthetic penicillins but not to natural penicillin. *Contact Dermatitis* 1991;25:192.
77. Rudzki E, Rebandel P, Glowacka M. Respiratory, food and contact hypersensitivity to penicillin (Article in Polish). *Pol Tyg Lek* 1985;40:1143-1145.
78. Rudzki E, Rebandel P, Grzywa Z. Patch tests with occupational contactants in nurses, doctors and dentists. *Contact Dermatitis* 1989;20:247-250.
79. Rudzki E, Rebandel P, Grzywa Z, Pomorski Z, Jakiminska B, Zawisza E. Occupational dermatitis in veterinarians. *Contact Dermatitis* 1982;8:72-73.
80. Rudzki E, Rebandel P, Rebandel B. Occupational allergy to antibiotics (Article in Polish). *Med Pr* 1986;37:383-387.
81. Schulz KH. Allergische berufsekzeme durch ampicillin [Allergic occupational eczemas caused by ampicillin]. *Berufsdermatosen* 1970;18:132-143.
82. Shinkai K, Nakamura K, Tsutsui N, Kuninishi Y, Iwaki Y, Nishida H, Suzuki R, Vohr HW, Takahashi M, Takahashi K, Kamimura Y, Maki E. Mouse popliteal lymph node assay for assessment of allergic and autoimmunity-inducing potentials of low-molecular-weight drugs. *J Toxicol Sci* 1999;24:95-102.
83. Shmunes E, Taylor JS, Petz LD, Garratty G, Fudenberg HH. Immunologic reactions in penicillin factory workers. *Ann Allergy* 1976;36:313-323.
84. Stejskal VD, Forsbeck M, Olin R. Side-chain-specific lymphocyte responses in workers with occupational allergy induced by penicillins. *Int Arch Allergy Appl Immunol* 1987;82:461-464.

85. Stejskal VD, Olin RG, Forsbeck M. The lymphocyte transformation test for diagnosis of drug-induced occupational allergy. *J Allergy Clin Immunol* 1986;77:411-426.

86. Van Krimpen PC, Van Bennekom WP, Bult A. Penicillins and cephalosporins. Physico-chemical properties and analysis in pharmaceutical and biological matrices. *Pharm Weekbl Sci* 1987;9:1-23.

87. Vil'sanskaja FL, Steinberg GB. Modification of the bacteria of the intestine and other organs following occupational exposure to antibiotics (streptomycin, tetracycline, penicillin). (Article in Russian, Abstract in English).*Gigiena truda i professional' nye Zabolevani* 1970;14:25.

88. Welch H. Problems of antibiotics in food as the Food and Drug Administration sees them. *Am J Public Health* 1957;47:701-705.

89. Wengrower D, Tzfoni EE, Drenger B, Leitersdorf E. Erythroderma and pneumonitis induced by penicillin? *Respiration* 1986;50:301-303.

90. Wright AJ. The penicillins. *Mayo Clin Proc* 1999;74:290-307.

91. Zent C. Drug allergy. *S Afr Med J* 1994;84:281-286.

17. Data bases used in search for literature

In the search for literature the following data bases were used:

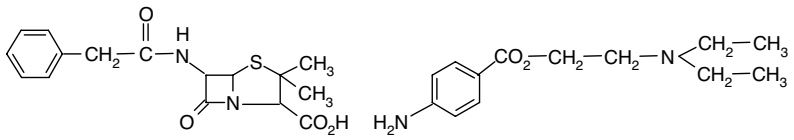
MEDLINE
NIOSHTIC
TOXLINE

Last search was performed in January 2000.

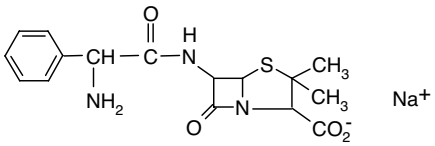
Submitted for publication May 26, 2004.

Appendix 1

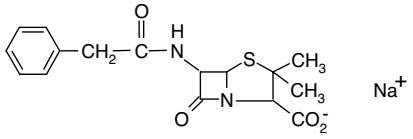
Chemical and physical properties of penicillins used in Sweden.

CAS No.	54-35-3
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- [2S-(2a,5a,6b)]-, compd. with 2-(diethylamino)ethyl 4-aminobenzoate (1:1)
Other chemical index names	Benzoic acid, 4-amino-, 2-(diethylamino)ethyl ester, mono[[2S-(2a,5a,6b)]-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] (9CI) 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd. with 2-(diethylamino)ethyl p-aminobenzoate (1:1) (8CI)
Synonyms/Trade names	Benzylpenicillin Novocaine; Benzylpenicillin novocaine salt; Benzylpenicillin procaine; Benzylpenicillin procaine salt; Benzylpenicillinum Procainum; Depocillin; Duphapen; Hostacillin; Hydracillin; Jenacillin O; Micro-Pen; Nopcaine; Penicillin G Procaine; Penzal N 300; Procaine Benzylpenicillin; Procaine benzylpenicillin salt; Procaine benzylpenicillinate; Procaine Benzylpenicillinum; Procaine Penicillin; Procaine Penicillin G; Retardillin; Vetspen; Vitablend
Molecular formula	$C_{16}H_{18}N_2O_4S.C_{13}H_{20}N_2O_2$
Molecular weight	571
Structural formula	
Physical state at 25°C	Solid white crystalline powder
Solubility	1 in 250 (water) 1 in 30 (ethanol) 1 in 60 (chloroform)

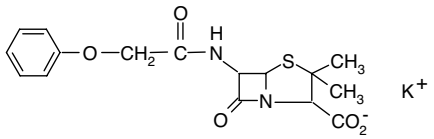
Chemical and physical properties of penicillins used in Sweden.

CAS No.	69-52-3
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(amino-phenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2S-[2a,5a,6b (S*)]]-
Other chemcial index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-, monosodium salt, D-(-)- (8CI)
Synonyms/Trade names	Alpen-N; Amcill-S; D(-)-alpha-Aminobenzylpenicillin sodium salt; Ampicillin-Na; Ampicillinnatrium; Ampicillinum Natricum; Ampicillin sodium; Ampicillin sodium salt; Anhypen; Binotal sodium; Britapen injection; Citteral; D-.alpha.-Aminobenzylpenicillin sodium salt; Domicillin; Monosodium ampicillin; Omnipen-N; PEN A/N; Penbritin-S; Penialmen; Polycillin-N; Principen/N; Sodium 6-[D-.alpha.-amino-phenylacetamido]penicillanoate; Sodium D-(-)-alpha-aminobenzyl-penicillin; Sodium D-.alpha.-aminobenzylpenicillanate; Sodium amipicillin; Sodium binotal; Sodium P-50
Molecular formula	$C_{16}H_{19}N_3O_4S.Na$
Molecular weight	372
Structural formula	
Physical state at 25°C	Solid off white powder
Melting point °C	205 with decomposition
Solubility	1 in 2 (water) 1 in 50 (ethane) Colloidal dispersion which gelts on standing is formed in ethanol

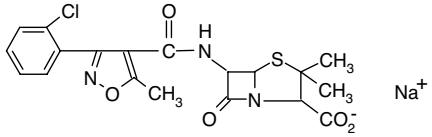
Chemical and physical properties of penicillins used in Sweden.

CAS No.	69-57-8
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- [2S-(2a,5a,6b)]-, monosodium salt
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, monosodium salt (8CI)
Synonyms/Trade names	American Penicillin; Benzylpenicillinic Acid Sodium Salt; Benzylpenicillin; Benzylpenicillin natr.; Benzylpenicillin Sodium; Benzylpenicillin Sodium Salt; Crystalline penicillin G; Crystapen; Monosodium benzylpenicillin; Mycofarm; Novocillin; Pen-A-Brasive; Penicillin-G, Monosodium Salt; Penicillin G; Penicillin G, Sodium; Penicillin G, Sodium Salt; Penilaryn; Sodium Benzylpenicillin; Sodium Benzylpenicillin G; Sodium 6-(phenylacetamido)penicillanate; Sodium Benzylpenicillinate; Sodium Penicillin; Sodium Penicillin G; Sodium Penicillin II; Veticillin
Molecular formula	$C_{16}H_{18}N_2O_4S.Na$
Molecular Weight	357
Structural formula	

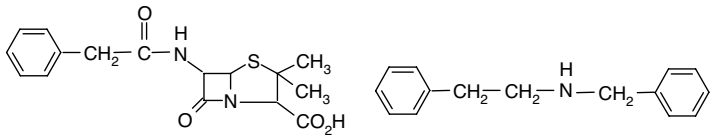
Chemical and physical properties of penicillins used in Sweden.

CAS No.	132-98-9
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(2-phenoxyacetyl)amino]-, monopotassium salt, [2S- (2a, 5a, 6b)]
Other CA index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenoxyacetamido)-, monopotassium salt (8CI);
Synonyms/Trade names	Abbopen; Antibiocin; Apsin VK; Arcacil; Arcasin; Beromycin; Beromycin 400; Beromycin (penicillin); Betapen-VK; Calciopen; Calciopen K; Cliacil; Compocillin-VK; Distakaps V-K; Distaquaine V-K; Dowpen V-K; DqV-K; Fenocin; Fenoxypen; Isocillin; Icipen; Ispenoral; Kavepenin; Kåvepenin; Ledercillin VK; Megacillin oral; Oracil-VK; Orapen; Ospeneff; Pedipen; Penagen; Pencompren; Penicillin potassium phenoxymethyl; Penicillin V potassium; Penicillin V potassium salt; Penicillin VK;Pen-Vee K; Pen-Vee K powder; PenVikal; Pfizerpen VK; D-alpha-phenoxymethylpenicillinate K salt; Phenoxymethylpenicillin potassium; Phenoxymethylpenicillin potassium salt; Potassium penicillin V; Potassium penicillin V salt; Potassium phenoxymethylpenicillin; Potassium phenoxymethylpenicillinate; PVK; Primcillin; Qidpen VK; Robicillin VK; Rocillin-VK; Roscopenin; SK-penicillin VK; Stabillin VK syrup 125; Stabillin VK syrup 62.5; Sumapen VK; Suspen; Tikacillin; V-Cil-K; Uticillin VK (V-Cillin K, Veetids, Vepen)
Molecular formula	$C_{16}H_{18}N_2O_5S.K$
Molecular weight	389
Structural formula	
Physical state at 25°C	Solid white crystalline powder
Melting point °C	263-265 with decomposition
Partition coefficient (Log P(o/w))	1.95 (37°C)*, unionised species -1.65 (37°C)*, ionised species
Solubility	1 in 1.5 (water) 1 in 150 (ethanol) practically insoluble in chloroform, ether and insoluble in acetone
Remarks	*Calculated values, (Tsuji et al)

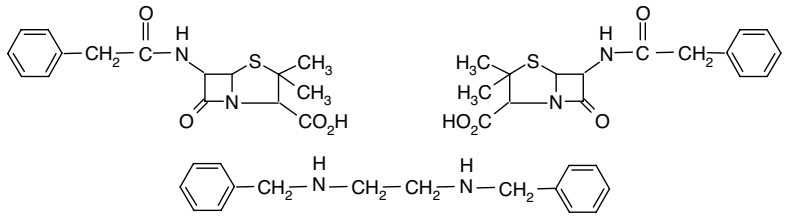
Chemical and physical properties of penicillins used in Sweden.

CAS No.	642-78-4
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2S-(2a,5a,6b)]-
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[3-(o-chlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-, monosodium salt (8CI)
Synonyms/Trade names	Alclox; Anaclosil; Ankerbin; Apo-Cloxi; Austrastaph; Bactopen; BRL 1621 sodium salt; Clocillin; Cloxacillin sodium; Cloxacillin sodium salt; Cloxapen; Cloxin; Cloxypen; Ekvacillin; Gelstaph; Landerclox; Monosodium cloxacillin; Novocloxin; Nu-Cloxi; Orbénine; Orbenin; Orbenin sodium; Prevencilina P; Prostaphilin A; Prostaphlin A; Sodium cloxacillin; Sodium orbenin; Sodium syntarpen; Staphybiotic; Syntarpen sodium salt; Tegopen
Molecular formula	$C_{19}H_{18}ClN_3O_5S.Na$
Molecular weight	459
Structural formula	
Physical state at 25°C	Solid white almost white powder
Solubility	1 in 2.5 (water) 1 in 30 (ethanol)
Remarks	Multi-ingredient preparations: Ampiclox, Amplium

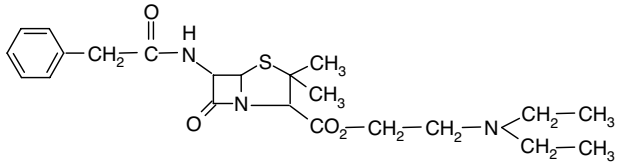
Chemical and physical properties of penicillins used in Sweden.

CAS No.	751-84-8
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- [2S-(2a,5a,6b)]-, compd. with N-(phenylmethyl)benzeneethanamine (1:1)
Other chemical index names	CN Benzeneethanamine, N-(phenylmethyl)-, [2S-(2a,5a,6b)]-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylate (9CI) Penicillin G, N-benzylphenethylamine salt (6CI) Phenethylamine, N-benzyl-, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate
Synonyms/Trade names	Benapen; Benetacil; Benethamine penicillin; Benethamine penicillin G; Benetolin; Benzylpenicillin N-benzyl-2-phenylethylamine salt; Benzylpenicillinic acid N-benzyl-.beta.-phenylethylamine salt; Betapen; N-Benzyl-2-phenylethylamine salt of benzylpenicillin; N-Benzylphenethylamine benzylpenicillin salt; Penicillin G benethamine
Molecular formula	$C_{16}H_{18}N_2O_4S.C_{15}H_{17}N$
Molecular weight	546
Structural formula	

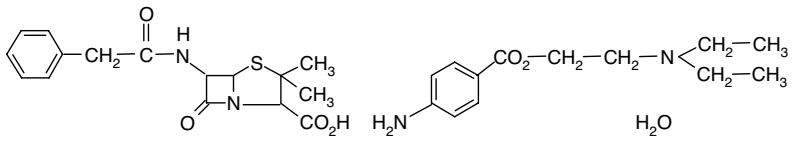
Chemical and physical properties of penicillins used in Sweden.

CAS No.	1538-09-6
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- [2S-(2a,5a,6b)]-, compd. with N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1)
Other chemical index names	1,2-Ethanediamine, N,N'-bis(phenylmethyl)-, bis[[2S-(2.a,5a,6b)]-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] (9CI) 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd. with N,N'-dibenzylethylenediamine (2:1) (8CI) Ethylenediamine, N,N'-dibenzyl-, bis[3,3-dimethyl-7-oxo-6-(2- phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate] (8CI) Penicillin G, N,N'-dibenzylethylenediamine salt (6CI)
Synonyms/Trade names	Ampicillin N,N'-dibenzylethylenediamine salt; Beacillin; Benzacillin; Benzapen; Benzathine Penicillin; Benzathine Benzylpenicillin; Benzathini Benzylpenicillinum; Benzathine penicillin G; Benzethacil; Benzilpenicillina Benzatinica; Benzylpencillin dibenzylethylenediamine salt; Benzylpenicillin benzathine; Benzylpenicillin N,N'-dibenzylethylenediamine salt; Benzylpenicillinum Benzathinum; Bica-penicillin; Bicillin; Bicillin 1; Bicillin I; Cepacilina; Cillenta; Debecillin; Debecylina; Diamine penicillin; Dibencil; Dibencillin; Dibenzylethylenediamine dipenicillin G; Duropenin; Ethylenediamine, N,N'-dibenzyl-, compd. with penicillin G (1:2); Extencilline; Extenicilline; Lentopenil; Longacilina; Longicil; Megacillin suspension; Moldamin; N,N'-Dibenzylethylenediamine bis[benzyl penicillin]; N,N'-Dibenzylethylenediamine salt of benzylpenicillin; Neolin; Pen-Di-Ben; Penadur; Pendepon; Penditan; Penduran; Penicillin G Benzathine; Penicillin G, compd. with N,N'-dibenzylethylenediamine (2:1); Penidural; Penidure; Penzaethinum G.NN-Dibenzylethylenediammonium bis[(6R)-6-(2-phenylacetamido)-penicillanate]; Permapen; Strepdipen-Suspension; Tardocillin; Vicin
Molecular formula	$(C_{16}H_{18}N_2O_4S)_2.C_{16}H_{20}N_2$
Molecular weight	909
Structural formula	

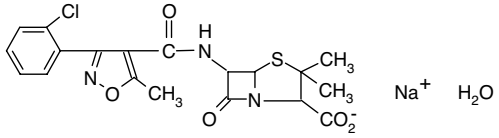
Chemical and physical properties of penicillins used in Sweden.

CAS No.	3689-73-4
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- [2S-(2a,5a,6b)]-, 2-(diethylamino)ethyl ester
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, 2-(diethylamino)ethyl ester (8CI) Penicillin G, 2-(diethylamino)ethyl ester (6CI, 7CI)
Synonyms/Trade names	Benzylpenicillin .beta.-diethylaminoethyl ester; Ephicillin; Penethamate; Penicillin G diethylaminoethyl ester
Molecular formula	$C_{22}H_{31}N_3O_4S$
Molecular weight	434
Structural formula	

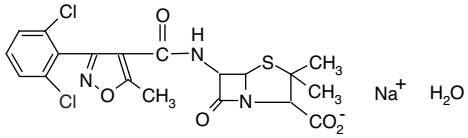
Chemical and physical properties of penicillins used in Sweden.

CAS No.	6130-64-9
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]- [2S-(2a,5a,6b)]-, compd. With 2-(diethylamino)ethyl 4-aminobenzoate (1:1), monohydrate
Other chemical index names	Benzoic acid, 4-amino-, 2-(diethylamino)ethyl ester, mono[[2S-(2.a,5a,6b)]-3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate], monohydrate (9CI) 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-, compd. with 2-(diethylamino)ethyl p-aminobenzoate (1:1), monohydrate (8CI) Benzoic acid, p-amino-, 2-(diethylamino)ethyl ester, mono[3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate], monohydrate (8CI)
Synonyms/Trade names	2-(4-Aminobenzoyloxy)ethyldiethylammonium (6R)-6-(2-phenylacetamido)penicillinate monohydrate; Procaine Penicillin; Abbocillin-DC; Afsillin; Ampin-pencillin; Aqucilina; Aquacillin; Aquasuspen; Avloprocil; Ayercillin; Benzylpenicillin procaine monohydrate; Cilicaine; Cilicaine Syringe; Cilina 900; Crysticillin; Depocillin; Despacilina; Distaquaine; Duracillin; Farmaproina; Flo-Cillin Aqueous; Kabipenin; Ledercillin; Millicillin; Mylipen; Neoproc; Novocaine penicillin; Novocillin; Pen-Fifty; Penaquacaine G; Pfizerpen-AS; Premocillin; Pro-Pen; Procaina; Procaine penicillin G hydrate; Procaine penicillin G monohydrate; Procanodia; Procillin; Prostabillin; Provipen; Quick-Cillin;Sharcillin; Wycillin
Molecular formula	$C_{16}H_{18}N_2O_4S.C_{13}H_{20}N_2O_2.H_2O$
Molecular weight	589
Structural formula	
Physical state at 25°C	Solid white crystalline powder
Solubility	1 in 250 (water) 1 in 30 (ethanol) 1 in 60 (chloroform)

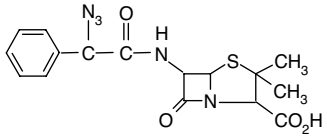
Chemical and physical properties of penicillins used in Sweden.

CAS No.	7081-44-9
Chemical index name (CA 9th CI)Chemical name	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2-chloro-phenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate, [2S-(2a,5a,6b)]-
Other chemical index name	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[3-(o-chloro-phenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate (8CI)
Synonyms/Trade names	Cloxacillin sodium monohydrate; Clocillin monohydrate; Cloxapen monohydrate; Sodium cloxacillin monohydrate
Molecular formula	$C_{19}H_{17}ClN_3O_5S.Na.H_2O$
Molecular weight	476
Structural formula	
Physical state at 25°C	Solid white almost white powder
Solubility	1 in 2.5 (water) 1 in 30 (ethanol)
Remarks	Multi-ingredient preparations: Ampiclox, Amplium

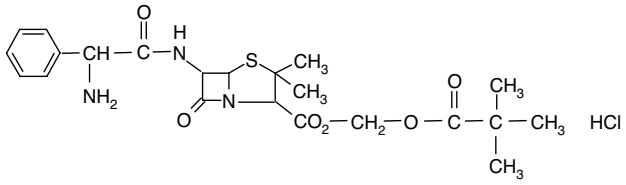
Chemical and physical properties of penicillins used in Sweden.

CAS No.	13412-64-1
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate, [2S-(2a,5a,6b)]-
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate (8CI);
Synonyms/Trade names	3-(2,6-Dichlorophenyl)-5-methyl-4-isoxazolyl penicillin sodium, monohydrate; Blp-1011; Brispen; Brl-1702; Constaphyl; Dichlorstapenor; Dichlorstapenor sodium; Diclocil; Dicloxacillin, sodium; Dicloxacillin sodium hydrate; Dicloxacillin sodium monohydrate; Dicloxacillin sodium salt; Dicloxacillin sodium salt hydrate; Dycill; Dynapen; Mdi-pc; Noxaben; P 1011; Pathocil; Pen-sint; Sodium dicloxacillin; Sodium dicloxacillin hydrate; Sodium dicloxacillin monohydrate; Stampen; Staphcillin a banyu; Syntarpen; Veracillin
Molecular formula	$C_{19}H_{16}Cl_2N_3O_5S.Na.H_2O$
Molecular weight	510
Structural formula	
Physical state at 25°C	Solid white or almost white hygroscopic crystalline powder
Solubility	Freely soluble in water, soluble in alcohol

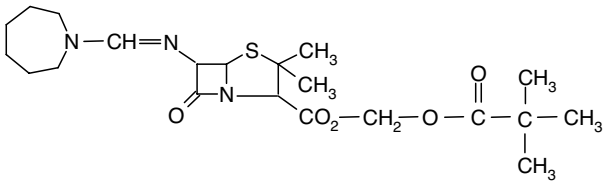
Chemical and physical properties of penicillins used in Sweden.

CAS No.	17243-38-8
Chemical name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(azidophenyl-acetyl)amino]-3,3-dimethyl-7-oxo-, [2S-[2a,5a,6b(S*)]]
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(2-azido-2-phenylacetamido)-3,3-dimethyl-7-oxo-, D-(-)- (8CI)
Synonyms/Trade names	Azidocillin; BRL 2534; D-(-)-.alpha.-Azidobenzylpenicilin; DAN 10510; Globacillin; SPC 297D
Molecular formula	$C_{16}H_{17}N_5O_4S$
Molecular weight	375
Structural formula	

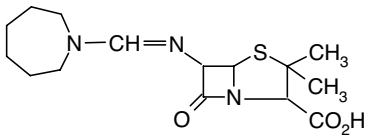
Chemical and physical properties of penicillins used in Sweden.

CAS No.	26309-95-5
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, monohydrochloride [2S-[2a,5a,6b (S*)]]
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-, hydroxymethyl ester pivalate (ester), monohydrochloride, D- (8CI); Methanediol, 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate pivalate (ester), monohydrochloride (8CI); Pivalic acid, hydroxymethyl ester 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, monohydrochloride (8CI)
Synonyms/Trade names	Alphacilina; Alphacillin; 6-(d-alpha-Aminophenylacetamido)penicillanic acid pivaloyloxymethyl ester; Hydrochloride; Ampicillin pivaloyloxymethyl ester hydrochloride; Ampicillin pivaloxyoxymethyl ester hydrochloride; Berocillin; Centurina; Devonium; Diancina; Inacilin; Maxifen; Pivaloyloxymethyl d-alpha-aminobenzylpenicillinate hydrochloride; Pivaloyloxymethyl ampicillinate; Pivaloyloxymethyl D-(-)-.alpha.-aminophenylacetamidopenicillanate; Pivampicillin hydrochloride; Pivatil; Pondocil; Pondocillin; Sanguicillin
Molecular formula	$C_{22}H_{29}N_3O_6S.HCl$
Molecular weight	500
Structural formula	
Remarks	Pondocillin is used for prepartion of tablets but not for granules

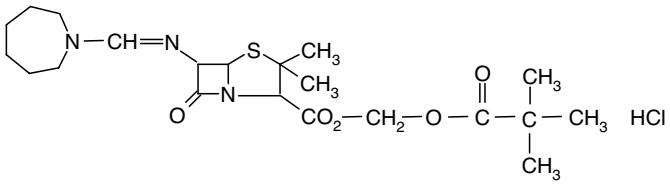
Chemical and physical properties of penicillins used in Sweden.

CAS No.	32886-97-8
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, [2S-(2a,5a,6b)]-
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-, hydroxymethyl ester pivalate (ester), (+)- (8CI)
Synonyms/Trade names	Amdinocillin pivoxil; FL 1039; Pivaloyloxymethyl (6R)-6-(perhydroazepin-1-ylmethyleneamino)penicillanate; Pivamdinocillin; Pivmecillinam more see Pivmecillinam; Selexid
Molecular formula	$C_{21}H_{33}N_3O_5S$
Molecular weight	440
Structural formula	

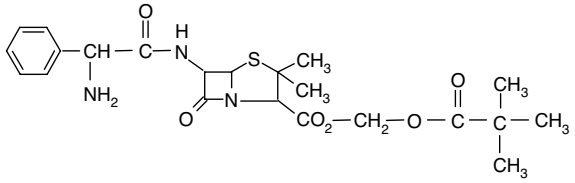
Chemical and physical properties of penicillins used in Sweden.

CAS No.	32887-01-7
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-, [2S-(2a,5a,6b)]-
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-, (+)- (8CI) 6-(perhydroazepin-1-ylmethyleneamino)penicillanic acid 4-Thia-1-Azabicyclo(3.2.0)Heptane-2-Carboxylic Acid, 6-(((Hexahydro-1h-Azepin-1-Yl)Methylene) Amino)-3,3-Dimethyl-7-Oxo-, (+)-
Synonyms/Trade names	6-((Hexahydro-1h-Azepin-1-Yl)Methyleneamino)Penicillanic Acid; Amdinocillin; Fl 1060; Hexacillin; Hexapen; Mecilinamo; Mecillinam; Penicillin Hx; Ro 10-9070; Selecidin; Selexid; Selexidin;
Molecular formula	$C_{15}H_{23}N_3O_3S$
Molecular weight	325
Structural formula	

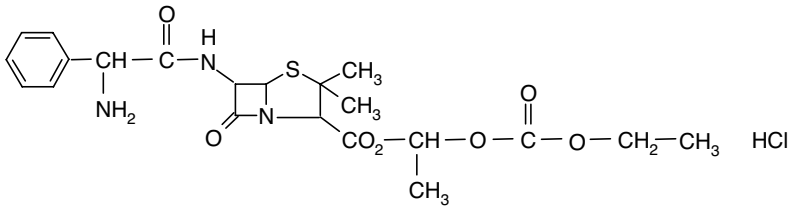
Chemical and physical properties of penicillins used in Sweden.

CAS No.	32887-03-9
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, monohydrochloride, [2S-(2a,5a,6b)]-
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-, hydroxymethyl ester pivalate (ester), monohydrochloride, (+)- (8CI)
Synonyms/Trade names	FL-1039; Melysin; Pivaloyloxymethyl (6R)-6-(perhydroazepin-1-ylmethyleneamino)penicillana te hydrochloride; Pivmecilinamo clorhidrato; Pivmecillinam Hydrochloride; Selexid
Molecular formula	$C_{21}H_{33}N_3O_5S.HCl$
Molecular weight	476
Structural formula	

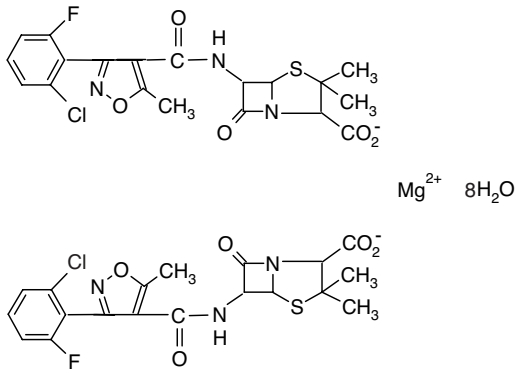
Chemical and physical properties of penicillins used in Sweden.

CAS No.	33817-20-8
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenyl-acetyl)amino]-3,3-dimethyl-7-oxo-, (2,2-dimethyl-1-oxopropoxy)methyl ester, [2S-[2a,5a,6b(S*)]]-
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-, hydroxymethyl ester pivalate (ester), D-(-)- (8CI)
Synonyms/Trade names	Alphacillin; Ampicillin pivaloyloxymethyl ester; MK 191; Pivaloyl-ampicillin; Pivaloyloxymethyl ampicillinate; Pivaloyloxymethyl D-.alpha.-aminobenzylpenicillinate; Pivampicillin*, Pondocillin**
Molecular formula	$C_{22}H_{29}N_3O_6S$
Molecular weight	464
Structural formula	
Remarks	Granulate is not called Pondocillin *Pondocillin is used as the product preparations name in Sweden though Pondocillin is the HCl salt of pivampicillin (CAS No. 26309-95-5) according to (RTECS) **According to RTECS this preparation contains pivampicillin HCl [26309-95-5]

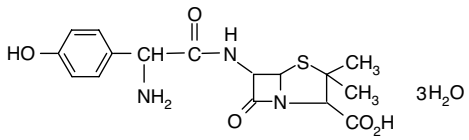
Chemical and physical properties of penicillins used in Sweden.

CAS No.	37661-08-8
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenyl-acetyl)amino]-3,3-dimethyl-7-oxo-, 1-[(ethoxycarbonyl)oxy]ethyl ester, monohydrochloride, [2S-[2a,5a,6b(S*)]]- 4
Synonyms/Trade names	Ambacamp; Ambaxin; Bacacil; Bacampicillin hydrochloride; BAPC; Becampicillin; Becampicillin hydrochloride; Penglobe; Spectrobid
Molecular formula	$C_{21}H_{27}N_3O_7S.HCl$
Molecular weight	502
Structural formula	
Physical state at 25°C	Solid white or practically white powder

Chemical and physical properties of penicillins used in Sweden.

CAS No.	58486-36-5
Chemical index name (CA 9th CI)	Magnesium, bis[6-[[[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl]-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylato-O2,O7]-, [T-4-[2S-(2a,5a,6b)], [2S-(2a,5a,6b)]]-
Other chemical index names	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, magnesium complex, [2S-(2a,5a,6b)]-
Synonyms/Trade names	Heracillin®; Magnesium flucloxacillin; Flucloxacillin, magnesum
Molecular formula	$(C_{19}H_{16}ClFN_3O_5S)_2.Mg.8H_2O$
Molecular weight	1074
Structural formula	

Chemical and physical properties of penicillins used in Sweden.

CAS No.	61336-70-7
Chemical index name (CA 9th CI)	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate, [2S-[2a, 5a,6b(S*)]]-
Synonyms/Trade names	alpha-Amino-p-hydroxybenzylpenicillin trihydrate; Amimox; Amoxicillin NM Pharm; Amoxicillin trihydrate; Amoxycillin trihydrate; Bristamox*; BRL 2333 trihydrate; Imacillin;
Molecular formula	$C_{16}H_{19}N_3O_5S,3H_2O$
Molecular weight	419
Structural formula	
Physical state at 25°C	Solid white (or almost white) crystalline powder
Partition Coefficient (Log P(octanol)**	0.87
Solubility	1 in 400 (water) 1 in 1000 (ethanol) practically insoluble in chloroform and ether
Remarks	*According to RTECS this preparations contains amoxicillin [26787-78-0] but the preparation sold in Sweden contains amoxicillin trihydrate [61336-70-7]. **Codex 1994 p.729

Appendix 2

Products that may cause potential penicillin exposure in the pharmacy: preparation of oral liquids.

Trade Name[a]	Type of product	Described State[2]	Marketing company
Phenoxymethylpenicillin (CAS No.: 132-98-9)			
Kåvepenin®	Mixture	Solid, granulate	Astra, Sweden
Kåvepenin®[b]	Dose granulate	Solid, granulate	Astra, Sweden
Kåvepenin®	Drops	Solid, granulate	Astra, Sweden
Amoxicillin trihydrate (CAS No.: 61336-70-7)			
Amimox®	Mixture	Solid, granulate	Tika, Sweden
Amoxicillin Scand Pharma	Mixture	Solid, granulate	Scand Pharma, Sweden
Imacillin®	Mixture	Solid, granulate	Astra, Sweden
Spetramox®[b]	Mixture	Solid, granulate	Astra, Sweden
Dicloxacillin sodium monohydrate (CAS No.: 13412-64-1)			
Diclocil	Mixture	Solid, powder	Bristol-Myers Squibb
Pivamecillinam (CAS No.: 32886-97-8)			
Selexid®	Dose granulate	Solid, granulate	Leo Pharma
Pivampicillin (CAS No.: 33817-20-8)			
Pondocillin®	Mixture	Solid, granulate	Leo Pharma
Pondocillin[b]	Dose granulate	Solid, granulate	Leo Pharma
Flucloxcillin (CAS No.: 58486-36-5)			
Heracillin®	Mixture	Nd[c]	Astra, Sweden

[a] Information taken from (53).
[b] Single dose granulate preparation is available for consumer to mix.
[c] Nd = not detailed