ISSN 1817-7077

FAO JECFA Monographs

12


# RESIDUE EVALUATION OF CERTAIN VETERINARY DRUGS

Joint FAO/WHO Expert Committee on Food Additives

75th meeting 2011

World Health Organization

Food and Agriculture Organization of the United Nations

FAO JECFA Monographs 12

# RESIDUE EVALUATION OF CERTAIN VETERINARY DRUGS

Joint FAO/WHO Expert Committee on Food Additives

75th Meeting

Rome, Italy, 8–17 November 2011



**FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS**
**WORD HEALTH ORGANIZATION**
Rome, 2012

ISBN 978-92-5-107255-4

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Joint FAO/WHO Expert Committee on Food Additives (JECFA)
Rome, Italy, 8–17 November 2011

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# ABBREVIATIONS

| | |
|---|---|
| ADI | Acceptable daily intake |
| ADME | Absorption, distribution, metabolism and excretion |
| AOAC | AOAC International |
| AUC | Area under the curve |
| BLQ | Below limit of quantitation |
| bw | body weight |
| CAC | Codex Alimentarius Commission |
| CAS | Chemical Abstracts Service |
| CCRVDF | Codex Committee on Residues of Veterinary Drugs in Foods |
| CL | Clearance rate |
| $C_{max}$ | Maximum concentration |
| CR | Clearance (Renal) |
| CV | Coefficient of variation |
| $C_{vr}$ | Reproducabilty |
| CRC | Controlled Release Capsule |
| ECD | Electron capture detector |
| EDI | Estimated daily intake |
| F | Bioavailability |
| FAO | Food and Agriculture Organization of the United Nations |
| GC | Gas chromatography |
| GLP | Good laboratory practice |
| h | hour |
| HPLC | High pressure liquid chromatography |
| i.m. | intramuscular [injection] |
| IR | Infrared |
| IUPAC | International Union of Pure and Applied Chemistry |
| i.v. | intravenous |
| JECFA | Joint FAO/WHO Expert Committee on Food Additives |
| JMPR | Joint FAO/WHO Meeting on Pesticide Residues |
| kg | kilogram ($10^3$ g) |
| L | litre |
| LC | Liquid chromatography |
| LOD | Limit of detection |
| LOQ | Limit of quantitation |
| LSC | liquid scintillation counting |
| µg | microgram ($10^{-6}$ g) |
| mg | milligram ($10^{-3}$ g) |
| min | minimum or minute |
| ml | millilitre |
| MRL | maximum residue limit |

| | |
|---|---|
| MRT | mean residence time |
| MS | mass spectrometry |
| MW | molecular weight |
| ng | nanogram ($10^{-9}$ g) |
| NOAEL | No observed adverse effect level |
| NQ | Non-quantifiable |
| QA | Quality assurance |
| QC | Quality control |
| RP | Reverse phase |
| rsd | Repeatability standard deviation |
| $R_t$ | retention time |
| s.c. | subcutaneous [injection] |
| SD | Standard deviation |
| SPE | Solid phase extraction |
| $t_{½}$ | Half life |
| TR | Total residue |
| TMDI | Theoretical maximum daily intake |
| TRR | total radiolabelled residues |
| UV | ultraviolet |
| VD | volume of distribution |
| $VD_{SS}$ | volume of distribution at steady-state |
| WHO | World Health Organization |

# INTRODUCTION

The monographs in this volume of the FAO JECFA Monographs on the residues of, statements on, or other parameters of the veterinary drugs on the agenda were prepared by the invited experts for the Seventy-fifth Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), held in Rome, Italy, 7–17-November 2011. This was the nineteenth meeting of JECFA convened specifically to consider residues of veterinary drugs in food-producing animal species. The Committee had evaluated residues of veterinary drugs at its 12th, 26th, 27th, 32nd, 34th, 36th, 38th, 40th,42nd, 43rd, 45th, 47th, 48th, 50th, 52nd, 54th, 58th, 60th, 62nd, 66th and 70th meetings (JECFA, various dates 1969–2010). The tasks for the Committee were to further elaborate principles for evaluating the safety of residues of veterinary drugs in food and for establishing acceptable daily intakes (ADIs) and recommend maximum residue limits (MRLs) for substances on the agenda when they are administered to food-producing animals in accordance with good veterinary practice in the use of veterinary drugs. The enclosed monographs provided the scientific basis for the recommendations of MRLs.

There is an important feature to bring to the attention of readers. This volume of the FAO JECFA Monographs is the third in a new format for the presentation of monographs from meetings of the Committee specifically devoted to residues of specific veterinary drugs in food. It was also the seventh meeting of JECFA subsequent to the completion of the workshop to update the principles and methods of risk assessment for MRLs for pesticides and veterinary drugs, held jointly by FAO/RIVM/WHO, in Bilthoven, The Netherlands, 7–11 November 2005. The outcomes of this workshop are incorporated in the Environmental Health Criteria, No. 240, publication *Principles and methods for the risk assessment of chemicals in food*, WHO, 2009. Specifically, the Committee continued to implement some of the more significant recommendations in the workshop report, including the concept of using median residue values to estimate daily intakes of residues of veterinary drugs in food for chronic exposure intake estimates.

## Background

In response to the growing use of veterinary medicines in food animal production systems internationally and the potential implications for human health and fair trading practices, a Joint FAO/WHO Expert Consultation on Residues of Veterinary Drugs was convened in Rome in November 1984 (FAO/WHO, 1985). One of the major recommendations of this consultation was the establishment of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) and the periodic convening of an appropriate expert body to provide independent scientific advice to this Committee and to member countries of FAO and WHO. At its first session, in Washington, DC, in November 1986, the CCRVDF reaffirmed the need for such a scientific body and made a number of recommendations and suggestions to be considered by JECFA (CCRVDF, 1986). In response to these recommendations, the 32nd JECFA meeting was devoted entirely to the evaluation of residues of veterinary drugs in food—a new responsibility for the Joint FAO/WHO Expert Committee on Food Additives. Nineteen such meetings of JECFA have been held prior to the meeting of JECFA reported here.

## 75th Meeting of JECFA

The present volume, in the new format, contains monographs on the residue data of seven of the substances scheduled for evaluation at the 75th Meeting of the Committee. Of the substances on the agenda, four were new evaluations (amoxicillin, apramycin, derquantel and monepental) and three were re-evaluations (monensin, narasin and triclabendazole). The re-evaluation of narasin was for a suitable analytical method in cattle tissues only. One substance, ivermectin, was originally scheduled for review by the Committee; however, there was no submission of new information regarding residues in food-producing animals on which to base any reconsideration of MRLs. The Committee noted that before it would re-evaluate the residue depletion of ivermectin and propose updated MRLs, it would need a submission indicating that a suitably validated analytical method with a limit of quantitation (LOQ) in the low µg/kg range for the marker residue has been used in the conduct of

depletion studies in fat, kidney, liver and muscle tissues of animals for which MRLs are requested. A literature review on the relevant toxicology to reconsider the acceptable daily intake (ADI) of ivermectin was conducted and a toxicological summary report was prepared for the Committee.

The monographs are prepared in a uniform format consistent with the data provided and the specific request for risk assessment by CCRVDF. The format includes identity of substance, residues in food and their evaluation, metabolism studies, tissue residue depletion studies, methods of residue analysis, a final appraisal of the study results, and if appropriate, recommendations on MRLs. A summary of the recommendations on compounds on the agenda and further information required is included in Annex 1. In addition, a summary of JECFA evaluations of residues of veterinary drugs in foods from the 32nd meeting to the present 75th meeting can be found in Annex 2.

The monographs and general considerations on risk assessment principles of this volume must be considered in the context of the full report of the meeting, which will be published in the *WHO Technical Report Series*.

On-line editions of *Residues of some veterinary drugs in animals and foods* (from FAO JECFA Monographs and *FAO Food and Nutrition Paper*, No. 41) are available. The monographs and statements that have been published in FAO JECFA Monographs No. 2 and this volume, as well as those published in *FAO Food and Nutrition Paper*, No. 41 (sixteen volumes since 1988) are all available online at http://www.fao.org/ag/agn/jecfa-vetdrugs/search.html. The search interface is available in five languages (Arabic, Chinese, English, French and Spanish) and allows searching for compounds, functional classes, ADI and MRL status.

### *Contact and feedback*

More information on the work of the Committee is available from FAO.

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**Use of JECFA reports and evaluations by registration authorities**

Most of the evaluations and summaries contained in this publication are based on unpublished proprietary data submitted to JECFA for use when making its assessment. A registration authority should not consider granting a registration based on an evaluation published herein unless it has first received authorization for such use from the owner of the data or any second party that has received permission from the owner for using the data.

# Amoxicillin

First draft prepared by
**Fernando Ramos**, Coimbra, Portugal
**Joe Boison**, Saskatoon, Canada
and
**Lynn G. Friedlander**, Rockville, MD, USA

## IDENTITY

**International Non-proprietary names (INN)**: Amoxicillin, formerly Amoxycillin

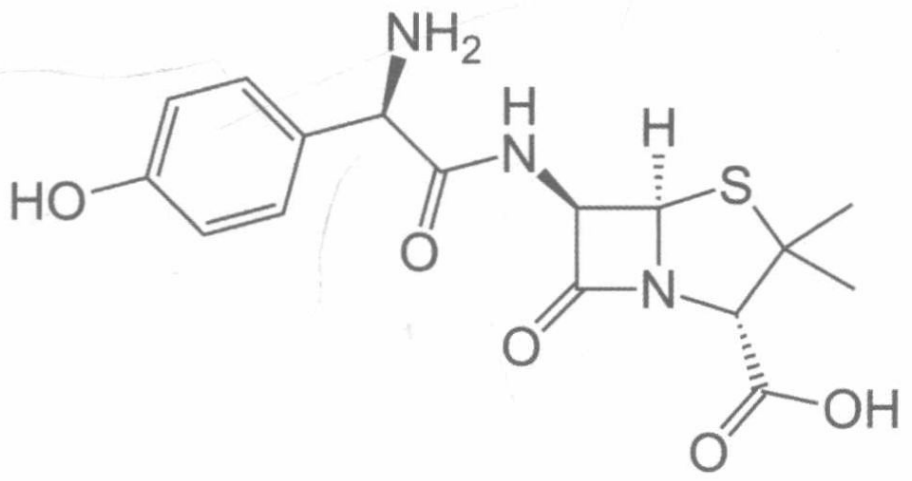
**Synonyms**: Amox; AMC; Amoxicillin trihydrate; Amoxicillin anhydrous; Amoxycillin trihydrate; D-Amoxicillin; p-Hydroxyampicillin

**IUPAC Names**: (2S,5R,6R)- 6-{[(2R)-2-amino- 2-(4-hydroxyphenyl)- acetyl]amino}- 3,3-dimethyl-7-oxo- 4-thia- 1-azabicyclo[3.2.0]heptane- 2-carboxylic acid

[2S - [2α,5α,6β(S*)]] - 6 - [[Amino (4 - hydroxyphenyl)acetyl]amino] - 3,3 - dimethyl - 7 - oxo - 4 - thia - 1 – azabicyclo [3.2.0] heptane - 2 - carboxylic acid

**Chemical Abstract Service No.**: Amoxicillin: 26787-78-0, Amoxicillin trihydrate: 61336-70-7

**Structural formula** of main components:




**Molecular formula:** $C_{16}H_{19}N_3O_5S$

**Molecular weight:** Amoxicillin: 365.40; Amoxicillin trihydrate: 419.41

## OTHER INFORMATION ON IDENTITY AND PROPERTIES

**Pure active ingredient:** Amoxicillin

**Appearance:** Powder/Crystalline solid

Melting point: 194°C

**pH**: 4.4–4.9 (0.25% w/v solution)

**Optical rotation:** +290°–315°

**Solubility:** 3430 mg/L water

**$UV_{max}$:** 272 nm (water)

**Partition coefficient:** -2.69

**Stability to acids and bases:** Amoxicillin is stable in the presence of gastric acid

# RESIDUES IN FOOD AND THEIR EVALUATION

## *Conditions of use*

Amoxicillin is a broad-spectrum, pharmacologically active beta-lactam antibiotic effective against Gram-positive and Gram-negative bacteria. Amoxicillin is stable in the gastro-intestinal tract and has higher absorption than naturally occurring penicillins when administrated orally. Amoxicillin is a widely used antibiotic in human and veterinary medicine for the treatment and prevention of respiratory, gastrointestinal, urinary and skin bacterial infections due to its pharmacological and pharmacokinetic properties (Sousa, 2005). Amoxicillin is de-activated by bacterial β-lactamase or penicillinases. In human medicine amoxicillin is commonly used in combination with clavulanic acid, a penicillinase inhibitor; it is not normally used with clavulanic acid in veterinary use.

Amoxicillin is used in many domestic and food animals, including cats, dogs, pigeons, horses, broiler chickens, pigs, goats, sheep, pre-ruminating calves (including veal calves) and cattle. In dogs and cats, amoxicillin is used in respiratory and urinary infections and in soft tissue wounds caused by Gram-positive and Gram-negative pathogenic bacteria (Pfizer, 2004). In poultry, amoxicillin is used for the treatment of susceptible infections of the alimentary, urogenital and respiratory tracts (APVMA, 2007). In pigs, amoxicillin is used to treat major respiratory tract pathogens, mainly caused by *Actinobacillus pleuropneumoniae*, *Streptococcus suis* and *Pasteurella multocida*. Amoxicillin also is used against some digestive and urinary tract pathogens, such as *Escherichia coli* and *Streptococcus suis* (Hernandez *et al.*, 2005; Reyns *et al.*, 2008a). In sheep, amoxicillin is used for the treatment of bacterial pneumonia due to *Pasteurella* spp. and *Haemophilus* spp. (FDA, 1999). In goats, amoxicillin is indicated for the treatment of respiratory tract infections caused by, among other microorganisms, *Mannheimia haemolytica, P. multocida, H. somnus,* but not for penicillinase-producing *S. aureus* (Baggot, undated). Amoxicillin also is used in pre-ruminating calves for treatment of bacterial enteritis due to *E. coli*, and in cattle for treatment of respiratory tract infections, including shipping fever and pneumonia due to *P. multocida*, *M. haemolytica, Haemophilus* spp., *Streptococcus* spp. and *Staphylococcus* spp., and for acute necrotic pododermititis (foot rot) due to *Fusobacterium necrophorum* (FDA, 2011). Amoxicillin is also approved for use in lactating dairy cows by intramammary infusion with a suspension of amoxicillin trihydrate containing the equivalent of 62.5 mg of amoxicillin per disposable syringe for each infected quarter (Schering-Plough, 2007).

## *Dosage*

In food-producing animals, amoxicillin is approved for use as amoxicillin trihydrate for oral suspensions equivalent to 40 mg amoxicillin twice daily for piglets under 4.5 kg; a soluble powder of amoxicillin trihydrate at 400 mg/45.5 kg body weight (bw) twice daily for pre-ruminating calves, including veal calves, administered by drench or by mixing in milk; amoxicillin trihydrate boluses containing 400 mg of amoxicillin per 45.5 kg bw for pre-ruminating calves, including veal calves; and as a sterile amoxicillin trihydrate powder for use as a suspension at 6.6–11 mg/kg bw once a day, administered by intramuscular (i.m.) or subcutaneous (s.c.) injection in cattle. For sheep, amoxicillin is approved for use as a sterile i.m. injection suspension containing 50 mg/ml at a dose rate of 7 mg/kg bw once a day; as a 150 mg/ml long-acting amoxicillin trihydrate oily i.m. injection suspension at 15 mg/kg bw every two days; and as a 200 mg/ml i.m. injection at 1 ml/20 kg bw for cattle, sheep and pigs (Virbac, 2008, 2011).

# PHARMACOKINETICS AND METABOLISM

## *Pharmacokinetics in laboratory animals*

### Rats

Amoxicillin was administered to 11 rats at 50 mg/kg bw as a bolus dose. Microdialysis samples were collected over 180 minutes to determine the amount of unbound drug in blood and muscle (Marchand *et al.*, 2005). A two-compartment pharmacokinetic model adequately described the unbound amoxicillin concentration-time profiles in both matrices. The results obtained are represented in

Figure 1.1. Amoxicillin was distributed rapidly and extensively within muscle and interstitial fluid, indicating that alterations in muscle blood flow seem unlikely to have a major effect on drug distribution characteristics.

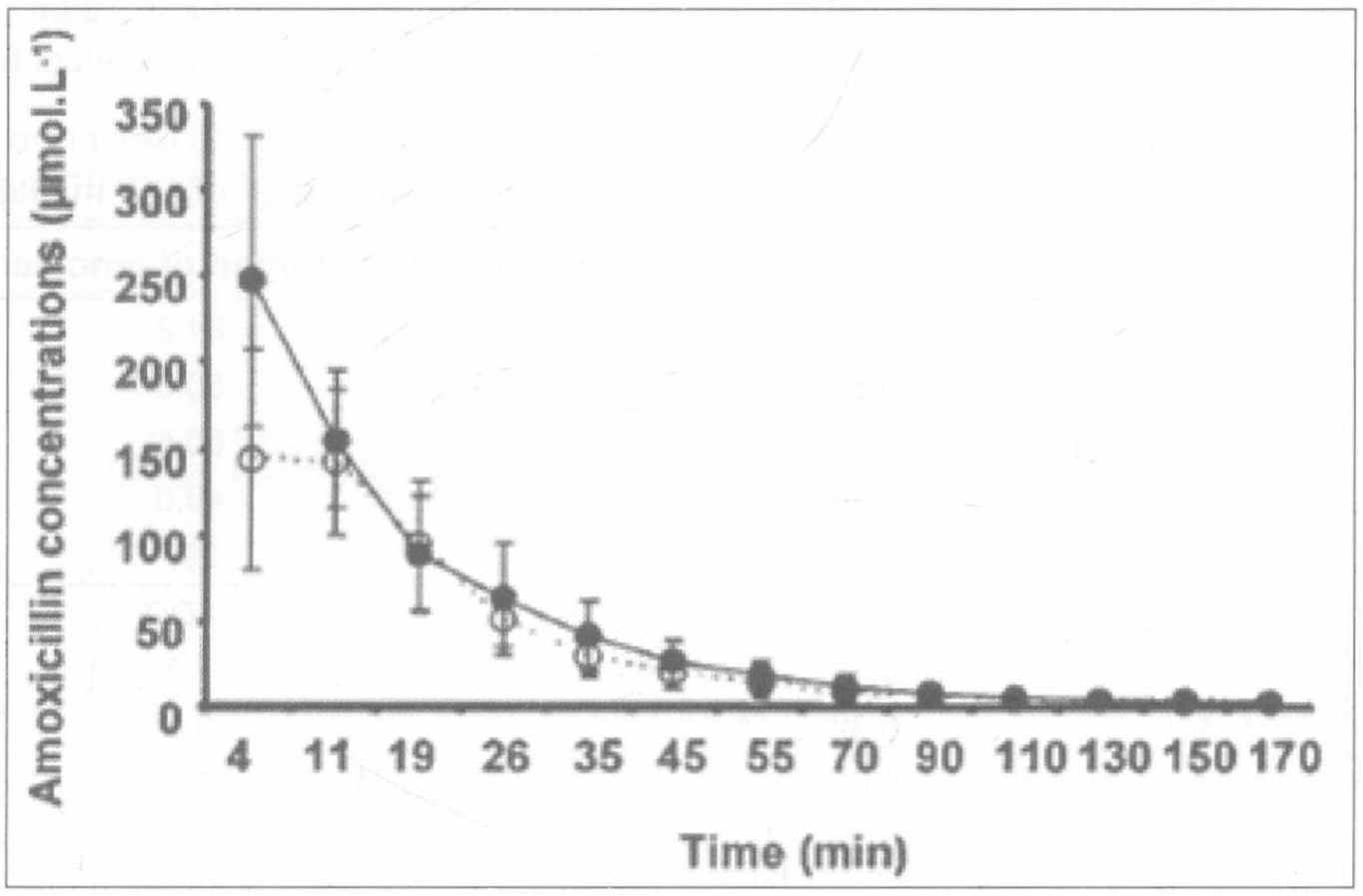



**Figure 1.1.** Unbound amoxicillin concentrations in blood and muscle of rats after intravenous (i.v.) bolus administration of amoxicillin at 50 mg/kg bw.
NOTES: Concentrations (mean ± SD) in blood (solid circles and solid line, n=11) and in muscle (open circles and dashed line, n=11)

Two pharmacokinetic studies were conducted to investigate the distribution of amoxicillin in rat tissues. In a Good Laboratory Practice (GLP)-compliant study using 12 healthy male Wistar rats, 3 h after a single oral administration of amoxicillin (15 or 60 mg/kg) the drug was distributed extensively in the microvilli, nuclei and cytoplasm of the absorptive epithelial cells of the intestine, in the cytoplasm and nuclei of the hepatocytes and on the luminal surface of the capillaries, intercalated portions, and interlobular bile ducts. Although almost no amoxicillin could be detected 6 h post-administration in either the intestine or the liver, it persisted until 12 h in the kidney (Fujiwara *et al.*, 2011). The second study (non-GLP-compliant) reported that, after a single oral dose of amoxicillin at 100 mg/kg to 6 rats, the drug distributed preferentially to liver and kidney (Sakamoto, Hirose and Mine, 1985).

### Dogs

Six dogs were dosed orally with three formulations of amoxicillin to evaluate the effect of drug formulation on oral bio-availability: a 60 ml suspension administered by an intragastric tube; 3 ml of amoxicillin drops; or in tablet form. The liquid forms of the drug tended to be more readily absorbed than the tablets (i.e. higher bio-availability) in comparison with that calculated for the suspension ($76.8 \pm 16.7\%$) and the drops ($68.2 \pm 25.8\%$) versus the tablets ($64.2 \pm 17\%$). However, the differences between their pharmacokinetic parameters ($C_{max}$, $t_{max}$ and AUC) were not statistically significant. The drops and tablets had similar pharmacokinetic profiles in the dogs and are regarded as equivalent in this species (Kung and Wanner, 1994).

Among a variety of species tested, amoxicillin distribution was independent of the binding percentage to plasma proteins (<40% in human, dog, rabbit, rat and mouse) (Sakamoto, Hirose and Mine, 1985).

## *Pharmacokinetics in food-producing animals*

### Fish

A study was conducted to determine amoxicillin residues in catfish muscle after oral administration (Ang *et al.*, 2000). Fish weighing 0.5–1.0 kg were maintained in indoor tanks prior to treatment. Using

a plastic pipette, 110 mg of amoxicillin/kg bw was administrated. Five fish were collected at each time interval for depletion periods up to 72 h post-dosing. Table 1.1 indicates the amoxicillin contents of individual fish after oral administration of the drug and depletion. All samples were analysed by a HPLC-Fluorescence method with a limit of quantitation limit (LOQ) of 1.2 µg/kg. Amoxicillin residues depleted rapidly from catfish during the first 24 h. After that the concentrations were <10 µg/kg, decreasing to <1.2 µg/kg after 72 h.

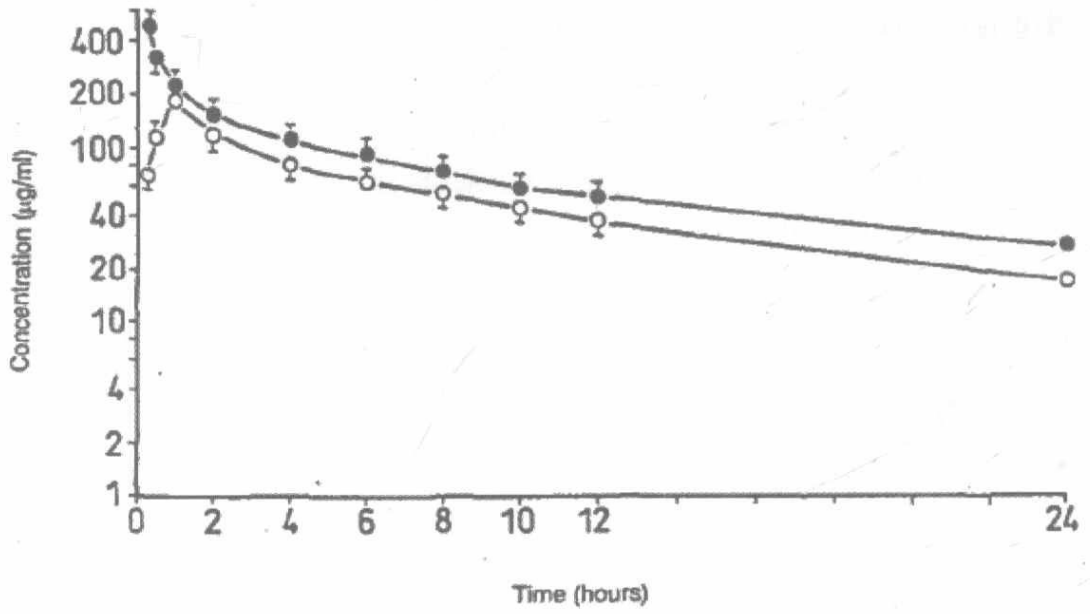
**Table 1.1.** Amoxicillin concentration in individual fish after oral administration of 110 mg/kg bw

| Depletion time (h) | Fish weight (kg) | Mean concentration of amoxicillin (µg/kg) |
|---|---|---|
| 6 | 0.76 | 64.2 |
| | 0.56 | 50.6 |
| | 0.38 | 60.5 |
| | 0.48 | 40.0 |
| | 0.66 | 297 |
| 24 | 0.38 | <LOQ |
| | 0.36 | 7.3 |
| | 0.32 | 3.7 |
| | 0.44 | 7.0 |
| | 0.52 | 7.9 |
| 48 | 0.50 | <LOQ |
| | 0.46 | 1.4 |
| | 0.54 | 6.9 |
| | 0.70 | 2.8 |
| | 0.38 | 1.9 |
| 72 | 0.48 | <LOQ |
| | 0.30 | <LOQ |
| | 0.44 | <LOQ |
| | 0.36 | <LOQ |
| | 0.36 | <LOQ |

## Chicken

Amoxicillin was given to two groups of eight chickens at a dose of 10 mg/kg bw, intravenously or orally (Anadón *et al.*, 1996). Blood samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h after drug administration. Plasma was separated and analysed by HPLC with UV detection. As can be seen in Figure 1.2, elimination profiles of amoxicillin were similar when administrated either i.v. or oral.

**Figure 1.2.** Plasma concentration of amoxicillin in chickens after intravenous (●) or oral (o) administration of 10mg/kg bw



Following oral administration, the maximum plasma concentration occurred at 1.00 ± 0.06 h with a $C_{max}$ of 160.40 ± 4.67 µg/ml (Table 1.2). Amoxicillin concentrations in plasma declined slowly and concentrations greater than 15 µg/ml persisted up to 24 h after oral administration (Figure 1.2). The values of the kinetic parameters that describe the absorption and disposition kinetics of amoxicillin are given in Table 1.2.

**Table 1.2.** Pharmacokinetic parameters (mean ± SD) of amoxicillin in eight chickens after intravenous or oral dosing of 10 mg/kg bw

| Parameter | Intravenous | Oral |
|---|---|---|
| $A_1$ (µg/ml) | 850.23 ± 21.95 | 220.04 ± 43.30 |
| $A_2$ (µg/ml) | 182.12 ± 8.72 | 107.53 ± 7.56 |
| $A_3$ (µg/ml) | | 342.54 ± 44.79 |
| $\alpha$ ($h^{-1}$) | 3.05 ± 0.11 | 0.77 ± 0.11 |
| $\beta$ ($h^{-1}$) | 0.086 ± 0.003 | 0.078 ± 0.005 |
| $K_a$ ($h^{-1}$) | | 2.39 ± 0.13 |
| $t_{½}\alpha$ (h) | 0.23 ± 0.01* | 1.00 ± 0.10 |
| $t_{½}\beta$ (h) | 8.17 ± 0.31 | 9.16 ± 0.60 |
| $t_{½a}$ (h) | | 0.30 ± 0.02 |
| $V_{d(area)}$ (L/kg) | 0.049 ± 0.002 | 0.054 ± 0.003 |
| $V_{d(ss)}$ (L/kg) | 0.042 ± 0.002 | |
| $K_{12}$ ($h^{-1}$) | 2.09 ± 0.09 | 0.31 ± 0.07 |
| $K_{21}$ ($h^{-1}$) | 0.61 ± 0.03 | 0.37 ± 0.04 |
| $K_{10}$ ($h^{-1}$) | 0.43 ± 0.03 | 0.16 ± 0.01 |
| AUC (mg/h/L) | 2449.3 ± 174.8 | 1534.6 ± 114.9 |
| F (%) | | 63.00 ± 4.58 |
| MRT (h) | 10.46 ± 0.51 | 12.26 ± 0.81 |
| CL (L/h/kg) | 0.004 ± 0.001 | 0.004 ± 0.001 |
| $K_{12}/K_{21}$ | 3.45 ± 0.12 | 0.83 ± 0.12 |
| $K_{12}/K_{10}$ | 5.02 ± 0.50 | 1.91 ± 0.30 |
| $K_{21}/K_{10}$ | 1.48 ± 0.17 | 2.40 ± 0.28 |
| $C_{max}$ (µg/ml) | | 160.40 ± 4.67 |
| $T_{max}$ (h) | | 1.00 ± 0.06 |

NOTES: * = Significantly different between dosing routes ($P$<0.05)

## Cattle

Six calves were fed milk replacer containing 0.25, 1.0 or 2.0 µg of amoxicillin/ml at 6% body weight twice daily, for three consecutive feedings (Musser *et al.*, 2001). Amoxicillin was quantified in serum and urine 3, 6, 9 and 15 h after drinking medicated milk replacer. By 24 h after the final feeding, no amoxicillin was detected in urine.

In a study with 8 pre-ruminating calves, three amoxicillin sodium preparations were compared for urinary excretion related to serum concentrations following i.m. administration (Palmer, 1975a). Although the serum profiles were different, renal clearance of approximately 200 ml/minute was observed at 2–8 h post-treatment and 48–52% of the administrated dose was recovered in the urine collected from 0–8 h post-treatment.

In the first formulation (aqueous suspension), 3 pre-ruminating calves received a dose of 7 mg/kg bw. An additional 3 pre-ruminating calves were treated with a 10.5 mg/kg bw oily suspension and the other 2 pre-ruminating calves were treated with a 7 mg/kg bw aqueous solution. Urine samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h. Total urine was collected for time periods 1–2 h, 4–6 h, 6–8 h and 8–24 h. Blood concentrations from the aqueous suspension produced mean peak serum concentrations of 2.0–2.5 µg/ml that was sustained for 6 h, declining to 1.5 µg/ml at 8 h. Animals

treated with the oily suspension showed a similar profile, with peak mean serum levels of 3.0 μg/ml at 2–3 h post dosing.

Pre-ruminating calves treated with the aqueous solution showed a peak mean serum concentration of 7.0–7.5 μg/ml 15 minutes post-treatment, and rapidly declined below the other formulations at 3 h post-treatment. Urine collections showed that 50–60% of the drug could be recovered from the urine in the 24 h following i.m. administration independent of the formulation used, with the majority of the excreted dose recovered in the first 8 h (48–52%). The quantity of amoxicillin excreted was proportional to the serum amount for a given urine collection period. Rates of renal plasma clearance were calculated (approximately 200 ml/min in plasma) for each product tested.

In a study of 16 pre-ruminating calves, amoxicillin was administered orally at 7 mg/kg bw. Two animals were slaughtered at each time point (0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h) and serum concentrations determined. Peak serum concentrations were 1.92–2.06 μg/ml at 2–3 h, declining to 0.2–0.4 μg/ml at 6–8 h post-treatment. Highest concentrations occurred in the alimentary tract. Concentrations persisted throughout the small intestine and colon for at least 8 h. Urine concentrations ranged from 6 μg/ml at 30 minutes to a peak concentration of 160 μg/ at 4 h. Amoxicillin concentrations were above 50 μg/ml from 1–12 h post-treatment (Palmer, 1975b; Palmer, Bywater and Francis, 1977).

Six calves were treated with an i.m. injection of amoxicillin at 7 mg/kg bw. Serum samples were collected at 0.25, 0.5, 1, 2, 3, 4 and 6 h post-treatment. Highest residues were in body fluids, bile and urine. Mean peak serum concentrations were 3.5–3.6 μg/ml at 1–2 h post treatment. High concentrations persisted in the small intestine for prolonged periods (Palmer, 1975c).

Sixteen pre-ruminating calves received an amoxicillin oral dose of 7 mg/kg bw administered with an oral doser using a 50 mg/ml formulated concentration. Two calves were slaughtered at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h post dose. Peak serum concentrations of 0.7–1.6 μg/ml were found at 4 h and declined to 0.3–0.4 μg/ml at 8 h post-treatment. High amoxicillin concentrations persisted in the small intestine for prolonged periods. Concentrations were approximately ten-fold higher in urine than in serum, although at maximum serum concentration, at approximately 4 h, the ratio was approximately six-fold higher. Peak urine concentration occurred at 8 h. Data indicate that only a small proportion of the dose is absorbed and distributed throughout the tissues when using the oral doser (Palmer, 1975d).

In another pharmacokinetic study in pre-ruminating calves, five animals were treated intravenously with sodium amoxicillin or sodium ampicillin at a dose of 7 mg/kg bw. Blood samples were collected from 15 min to 8 h and assayed using a microbiological method. Results were best fitted by a bi-exponential curve and a two compartmental model. The total volume of distribution was the same for amoxicillin or ampicillin (96%). The serum half-life for the terminal phase for amoxicillin (91 ± 5 min) was longer than for ampicillin (73 ± 7 min) (Palmer, 1976).

## Pigs

Several pharmacokinetic studies were conducted in pigs in which animals were treated with amoxicillin by different routes of administration: intravenous (i.v.), i.m. or oral. After i.v. administration, amoxicillin is rapidly distributed and eliminated, as suggested by the low values for volume of distribution at steady-state ($VD_{SS}$) and its low mean residence times (MRT). Different absolute bio-availability percentages were calculated after oral administration, ranging from 11 to 50%, depending on the formulation type and administration under fed or fasting conditions.

A GLP-compliant comparative cross-over trial was performed in pigs treated with amoxicillin by i.v., i.m. and oral routes in order to investigate the bio-availability of various drug formulations, including: a sodium salt for reconstitution in water and administered intravenously, a trihydrate salt in an oil base administered intramuscularly to produce a conventional duration of plasma concentrations; a trihydrate salt in oil base administered intramuscularly to product a prolonged duration of plasma concentrations; and a trihydrate powder for oral administration as a solution. The concentrations of amoxicillin in plasma were measured by HPLC-Fluorescence and its pharmacokinetic variables were assessed for the individual pigs, using non-compartmental methods. Following i.v. administration (8.6 mg/kg bw), amoxicillin was rapidly eliminated with a MRT of 1.4 h. After i.m. administration of the conventional formulation (14.7 mg/kg bw), the plasma amoxicillin concentration peaked at 2 h at