



Title	Development of analytical method for antibiotic residues in food and environmental water
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## 論文内容の要旨

氏 名 ( Nguyen Van Sy )	
論文題名	Development of analytical method for antibiotic residues in food and environmental water (食品・環境水中の残留抗菌性物質の分析法開発に関する研究)
論文内容の要旨	
<p>In recent years, antibiotic-resistant bacteria (ARB) have become a serious problem worldwide. One of the causes of ARB generation and spread is over-use of antibiotics for not only medications for human but also livestock and fishery productions. Therefore, it is important to monitor antibiotic residues in food and environment to prevent ARB issues. In Vietnam, aquacultural and agricultural productions are growing rapidly. The consumption of medications, including antibiotics, by both livestock and aquatic animals has also increased. However, knowledge regarding proper antibiotic use is limited; and many kinds of antibiotics have been abused and even used illegally by both farmers and veterinarians.</p> <p>First, in order to understand current situation of antibiotic residues in Vietnamese environment, antibiotics including sulfonamides, quinolones, <math>\beta</math>-lactams, tetracyclines, and others were monitored in 109 environmental water samples in Ha Noi, Thai Binh, and Can Tho. Among 49 target compounds, sulfamethoxazole (SMX, 68/109, 62%), sulfadimidine (SDD, 48/109, 44%), N-acetyl sulfadimidine (40/109, 37%), flumequine (28/109, 26%), trimethoprim (31/109, 28%), and cephalixin (30/109, 28%) were frequently detected in the water samples. <math>\beta</math>-lactam antibiotics including ampicillin (ABPC) seldom were detected. However, by observation study, it was disclosed that consumption of <math>\beta</math>-lactams was high. Therefore, the novel method for monitoring <math>\beta</math>-lactams discharged into environment was required.</p> <p>Next, the method was developed to detect 2-hydroxy-3-phenylpyrazine (HPP), one of the degradation products of ABPC and other <math>\beta</math>-lactam antibiotics with an ABPC substructure, in environmental water. The method involves extraction of HPP from water samples by using a solid-phase extraction cartridge and measurement by liquid chromatography/tandem mass spectrometry. The limit of quantification was 1 ng/L. The recovery rates of HPP from water samples were 84.1 - 86.1% (spiked levels of 25 and 125 ng/L, respectively). This method was then applied to evaluate HPP residual levels in 98 water samples collected from rivers, household ponds, and aquacultural ponds in Vietnam, with HPP detected in 60 of the samples. The concentration of HPP residue ranged from 1.3 to 413.3 ng/L. The results of this study indicated that ABPC and some other <math>\beta</math>-lactam antibiotics with an ABPC substructure had been used and released into the environment near the sampling sites.</p> <p>Finally, a method using ion-pair chromatography with fluorescent detection to detect the residues of seven penicillins in chicken muscle was developed. This method involved extraction of the penicillins with sodium tungstate and sulfuric acid followed by cleanup and concentration on a solid phase extraction cartridge. The eluate from the cartridge was reacted with 1-bromoacetyl pyrene to form fluorescent derivatives, which were then analyzed with HPLC-FLD. Seven analytes were separated on an C18 column by elution with a mobile phase containing ion-pairing sodium lauryl sulfate with methanol and acetonitrile. The method was fully validated according to the AOAC. The developed method could be satisfactorily applied as a routine procedure to detect penicillin residues in laboratories of food quality and safety control.</p> <p>In this thesis, a new analytical method was developed and validated to detect an antibiotic degradation product in the environment in Vietnam. Besides this, I also developed a new method for analysis of penicillin residue in food. The results of this thesis will act as a basis for proposing a sustainable monitoring system of antibiotic residues in food and the environment to the Vietnamese government. The monitoring system might help prevent the spread of ARB in Vietnam.</p>	

## 論文審査の結果の要旨及び担当者

氏 名 ( Nguyen Van Sy )	
	(職) 氏 名
論文審査担当者	主 査 教授 平田 収正 副 査 教授 上島 悦子 副 査 教授 高木 達也
<b>論文審査の結果の要旨</b>	
<p>東南アジアにおいて脅威となっているESBL (Extended Spectrum <math>\beta</math> Lactamase) 産生菌等の多剤耐性菌の高頻度な出現は、現地での畜水産業における抗生物質の無秩序な使用が主原因である。博士論文「Development an analytical method to detect antibiotics residue in food and environment in Vietnam」では、多剤耐性菌の出現防止に向けて、東南アジアで広くかつ大量に使用されている<math>\beta</math>ラクタム系抗生物質に対して高感度かつ網羅的に適用でき、環境モニタリングにも用いることができる機器分析法の開発を目指すものであり、LC/MS/MS等を用いた新規検出法の開発に成功した。</p> <p>具体的には、まず東南アジアで使用頻度が高い数種の<math>\beta</math>ラクタム系抗生物質について、カラム、移動相等の条件の最適化により、一斉分析により高感度かつ高精度で分離・定量ができる分析条件を確立した。様々な抗生物質が混在する実環境において実用性の高い当該抗生物質モニタリング法として期待できる。また、現地で使用されている代表的な<math>\beta</math>ラクタム系抗生物質であるアンピシリンについて、比較的安定で特異的な代謝産物であるHPPの高感度な検出条件を確立した。アンピシリンは環境中での速やかに分解されるために環境での検出が難しいことから、本法は多剤耐性菌出現を防止する上で非常に重要な監視対象物質であるアンピシリンの環境モニタリングに有用である。</p> <p>本研究の成果は、今後東南アジア等の発展途上異国において使用される<math>\beta</math>ラクタム系抗生物質に対する実用的な環境モニタリングシステムの開発につながる有用な機器分析法を開発したことにあり、また個々の抗生物質の細微な物性の違いに基づく分析方法を確立した点は学術的価値も高い。以上、これらの点についての審査により、博士 (薬科学) の学位論文に値するものと認める。</p>	