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# Surveys on Banned Veterinary Drugs Residues in Marine Bivalves and Gastropods in Taiwan between 2010 and 2015: A Mini Review

**Geng-Ruei Chang***

Department of Veterinary Medicine, National Chiayi University, Taiwan

***Corresponding author:** Geng-Ruei Chang

grchang@mail.ncyu.edu.tw

Department of Veterinary Medicine, National Chiayi University, Chiayi, Taiwan.

**Tel:** 886-5-2732946
**Fax:** 886-5-2732917

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## Abstract

Food safety in aquaculture is a crucial public health concern worldwide. Although Taiwan is a small island, the superior aquaculture techniques it employs allow Taiwan to maintain competitiveness in the Asian region. To achieve greater productivity, Taiwan's aquacultures prefer intensive large-scale breeding operations, which can increase susceptibility to numerous pathogens. The use of several chemical substances with antimicrobial activity may be necessary to prevent and treat microbial and parasitic diseases. Because of this, residues of banned veterinary drugs namely chloramphenicol, malachite green and leucomalachite green and nitro furan metabolites may be present in shellfish available for consumption. Their toxicity for consumers, as well as their potential impact on the environment, could raise barriers to commercialization within Taiwan and for export. The objective of this review was to provide context and evidence for the use of banned agents in cultured shellfish, such as hard clams, freshwater clams, abalones and sea ears. Culturing of these shellfish emerged in Taiwan in the 1990s. Special attention was devoted to detecting the residual levels and violated ratios of illegally used animal drugs in shellfish products between 2010 and 2015. The results of these surveys indicated that the Taiwanese population is exposed to low (ng/g) concentrations of some banned veterinary drug residues, such as chloramphenicol, AOZ and SEM, through their consumption of shellfish. Among these samples, the highest ratio of positive identification of banned veterinary drugs was 12.8% of 39 samples in 2011, however, the residues were in trace amounts, with no immediate risk to consumer health. Therefore, continual monitoring of aquatic products is necessary to ensure food safety. Furthermore, these findings act as a reference for the health and agriculture authorities for improving administration and regulation.

**Keywords:** Banned veterinary drugs; Residues; Shellfish; Taiwan; Violated ratio

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## Introduction

Aquaculture in Taiwan has a long history of more than three centuries and it has expanded rapidly, diversified, intensified and technologically advanced through spectacular times from 1960 to 1990s. Despite being a small island, Taiwan is one of the major distant water fisheries and aquaculture producers in the world [1]. Limitations of Taiwan's land and water resources, this remarkable accomplishment in marine production was astounding, it therefore was once called "kingdom of aquaculture" [2]. Until now, there were over 30 major and candidate species for commercial culture [3]. These include fishes, bivalves, gastropods, crustaceans, reptiles, amphibians and seaweeds. The average of economic advantage in cultured marine reached to US $11 billion between 2010 and 2015 [3]. Moreover, annual aquaculture production was around 40,000,000 during the 2010s. Specifically, the productions and values of culturing bivalves and gastropods are notably achievement because Taiwan's government strongly supports these aquacultures since 1990s.

In light of land use, Taiwan's aquaculturers prefer large-scale and intensive breeding operations [4]. As cultures trended to stocking densities contributed to increase difficult in the management of water quality and maintenance of the culture environment.

These cultured species became more susceptible to bacterial, parasitical and fungal infections, necessitating the use of various veterinary drugs for their prevention and treatment. However, heavy use of veterinary drugs in aquaculture may lead to the residues of aquaculture products, other unintended ecological consequences and increase public health concerns, such as an increasing the risk of allergies, developing antibiotic-resistant bacteria and increasing carcinogenic risk in humans [5]. In this regard, aquaculture products have played an important role in food safety.

Bivalves, such as hard clams (*Meretrix lusoria*) and freshwater clams (*Corbicula fluminea*), gastropods, such as abalone (*Haliotis discus*) and sea ear (*Haliotis diversicolor aquatilis*) are the most widely and emergingly cultured shellfishes in land-based ponds in Taiwan [6,7]. Their cultivation methods in the inner regions of Taiwan typically involve mixed breeding with other aquatic products or polyculturing with waterfowls. They can easily accumulate chemicals through preventing or treating diseases in non-shellfish targets. Based on veterinary drugs residues in marine are a crucial public health concern, particularly when banned chemicals are used illegally. Therefore, in the presenting paper, we summarized the residues of banned veterinary drugs banned in Taiwan, namely chloramphenicol, malachite green, leucomalachite green and nitrofuran metabolites, in marketed and aqua cultural shellfish samples. These data on the topic came from 2010 to 2015, which remarkably surveyed the veterinary drug residues in aquatic products. The concise information obtained is useful in evaluating the safety of seafood and provided to health authorities as a reference for direction.

# Banned Veterinary Drug Residues in Shellfish

## Chloramphenicol

Chloramphenicol is a broad-spectrum antibacterial agent and commonly used in aquaculture in Taiwan to control bacterial diseases. Accumulating reports indicate that one of its side effects is aplastic anaemia in humans, which has resulted in its limited usage [8]. In 1969, the Joint FAO/WHO Expert Committee on antibiotics suggested zero tolerance of chloramphenicol residues [9]. Numerous countries including the United States, Canada, Australia and European Union (EU) member states have prohibited its use in food animals [10]. Moreover, the Ministry of Health and Welfare of Taiwan banned the administration of chloramphenicol to food animals in 2002, with a maximum residual level (MRL) of zero. Before that time, chloramphenicol residue levels from 1 to 10 ng/g were permitted in food of animal origin. However, illegal usage consequently led to serious concerns regarding excessive medication in Taiwan's fish farming industry in the early 2000s. Drug residues in aquaculture products have been detected and rejections of consignments of products have occurred. For example, in 2003 the EU detected chloramphenicol residues in tilapia products from Taiwan.

The Taiwan Food and Drug Administration (TFDA) conducted surveys of chloramphenicol in bivalve samples. No chloramphenicol residues were detected in 10 samples in 2010, 29 samples in 2011, 18 samples in 2012, 20 samples in 2013, 34 samples in 2014 and 20 samples in 2015 [11-16]. In addition, the surveys did not positively identify chloramphenicol residues in gastropod products in 9 samples in 2010, 10 samples in 2011, 10 samples in 2012, 19 samples in 2013, 23 samples in 2014 and 11 samples in 2015, respectively. However, in my previous report, one hard clam sample tested positive for chloramphenicol at 3.8 ng/g and the ratio of positive identification was 3.9% in 26 bivalve samples collected in 2012 [4]. These results revealed that chloramphenicol has not been widely used in Taiwan's shellfish aquaculture in recent years. This may be because of the legal prohibition by Taiwan's government. Furthermore, we suggest that mixed breeding has resulted in the detection of chloramphenicol used to prevent and treat infectious diseases of other aquatic products (e.g., milkfish) and waterfowls (e.g., ducks) through drugs incorporated into feed. We could not locate any overseas reports on residual chloramphenicol in bivalves or gastropods; however, residual chloramphenicol has been detected in shrimp samples in Vietnam, India, Bangladesh and Thailand and China [17-20]. These results showed a continuation of chloramphenicol use because of its ready availability and ability to treat or prevent disease outbreaks, as well as inadequate management in improving the health status of cultured organisms in developing Asian countries **(Table 1)**.

## Malachite green and leucomalachite green

Malachite green is a triphenylmethane dye used extensively in aquaculture because of its low cost, ready availability and efficiency in preventing and treating external fungal and parasitic infections [21]. It was widely used in Taiwanese aquaculture as an anti-mould agent in water between the 1950s and 1990s. Marine life easily absorbs malachite green through waterborne exposure and rapidly metabolizes it into leucomalachite green. This reduction derivative accumulates in the edible muscle tissues of aquatic products over a period of months. However, studies have shown that malachite green and leucomalachite green may cause carcinogenesis, mutagenesis, chromosomal fractures, teratogenesis and respiratory toxicity in animals [16,22]. Therefore, malachite green is either highly restricted or banned for any aquaculture use in numerous countries, including EU states, the United States, Canada, China and Japan. Additionally, the Ministry of Health and Welfare of Taiwan declared in the regulations set forth in Tolerances for residues of veterinary drugs (2001) that malachite green and leucomalachite green must not be present in shellfish products because of toxicological considerations. However, illegal use of malachite green continues worldwide in aquaculture because of its low cost and ready availability. For example, malachite green was detected in farmed grouper fish in Taiwan in September 2005. This severely affected the fish farming industry in South Taiwan because imports of the fish into Hong Kong were halted [23]. In another notable example, Japan adopted measures to limit Chinese eel imports because of numerous instances of malachite green and leucomalachite green detection in Chinese eels between 2008 and 2010. Japan passed serious trade protection laws regarding aquatic products after these incidents.

In total, the TFDA analyzed 20 hard clam, 16 freshwater clam, 7 abalone and 12 sea ear samples in 2013, 20 hard clam, 14 freshwater clam, 12 abalone and 11 sea ear samples in 2014 and 20 hard clam and 11 sea ear samples in 2015 [14-16]. No malachite green or leucomalachite green residues were detected in these shellfish samples. In addition, my previous report indicated the absence of malachite green and leucomalachite green residues in 17 hard clam and 9 freshwater clam samples [4]. However, leucomalachite green was detected in six fish samples and one soft-shell turtle sample in 2014, the levels of residues ranged from 1.1 ppb to 90.4 ppb [15]. The violated ratio of leucomalachite green residue for these samples was lower than 3%. Moreover, the trace residues may have been caused by contamination from residues previously deposited in water bodies or sediments in aqua farms [16]. The Ministry of Health and Welfare of Taiwan gave the incident a yellow warning sign because scientific evidence showed that malachite green does not do serious damage to human health, however, the public should be alerted. Taiwan's consumers can visit the Food Information website at http://www.fda.gov.tw to access food safety information at any time. From the obtained information, it is concluded that exposure to malachite green and leucomalachite green residues in aquatic products through human consumption should be avoided.

## Nitrofurans and nitrofuran metabolites

Nitrofurans-including furazolidone (FZD), nitrofurazone (NFZ), nitrofurantoin (NFT) and furaltadone (FTD), are broad-spectrum antibacterial drugs that contain a 5-nitrofuran ring and various substituents in the 2-position [24]. In addition to their common use as veterinary drugs to treat protozoan and bacterial infections, they are frequently used in animal husbandry as feed additives for poultry, pigs, cattle, cultured fish and shrimps. Nitrofurans are short-lived once they have been consumed and are rapidly metabolized into tissue-bound, toxic metabolites within a few hours. These metabolites are strongly bound to proteins and highly stable for long periods (several weeks or even months), which can be utilized in the analysis of nitrofuran residues in food. The most crucial metabolites are 5-methylmorpholino-3-amino-2-oxazolidinone, 3-amino-2-oxazolidinone (AOZ), 1-aminohydantoin and semicarbazide (SEM), which are derived from furaltadone, furazolidone, nitrofurantoin and nitrofurazone, respectively [25]. Nitrofurans and their metabolites have displayed significant toxicity in humans that is manifested through carcinogenic, mutagenic and teratogenic effects [26]. For this reason, the application of nitrofuran compounds in food and animal production has been banned in the EU since 1995 and the United States since 2002 [27]. Additionally, in Taiwan, nitrofurans have been strictly prohibited for use in animal husbandry since 2004 because of their negative impact on food safety and international trade [28]. However, because of their efficiency, availability and low cost, the illegal or imprudent use of nitrofurans still occurs. In recent surveys, residues of nitrofuran metabolites were detected in fish and shrimps purchased between 2000 and 2004 from numerous Asian countries, including Thailand, Vietnam and China [29,30]. A further example occurred in 2000, when aquaculture exports from Taiwan were rejected or destroyed on site for sanitation reasons, because tilapia and processed eel exported to Europe were found to contain nitrofuran metabolite residues. The resulting trade restrictions prompted many food producers and regulatory authorities in Taiwan to instigate nitrofuran-monitoring schemes.

To detect nitrofuran metabolite residue, the TFDA analyzed 19 samples (10 hard clam and 9 abalone) in 2010, 39 samples (29 hard clam and 10 abalone) in 2011, 39 samples (18 bivalve, 10 abalone and 11 sea ear) in 2012, 55 samples (20 hard clam, 16 freshwater clam, 7 abalone and 12 sea ear) in 2013, 57 samples (20 hard clam, 14 freshwater clam, 12 abalone and 11 sea ear) in 2014 and 31 samples (20 hard clam and 11 sea ear) in 2015 [11-16]. From these surveys, five positive results were observed with AOZ ranging from 2.9 to 27.7 ng/g detected in hard clam samples screened in 2011. In 2012, one sea ear sample was found to contain detectable levels of AOZ (14.9 ng/g) and SEM (4.1 ng/g). In addition, a sea ear sample tested positive for detectable levels of SEM (2.0 ng/g) in 2013. The violated ratio for nitrofuran metabolite residues in shellfish samples was 0% in 2010, 12.8% in 2011, 2.6% in 2012, 1.8% in 2013 and 0% in 2014 and 2015. By contrast, the violated ratio for nitrofuran metabolite residues in bivalve samples was 0% for the 17 hard clam and 9 freshwater clam samples in my previous report [4]. The differences between reports can partly be explained by sample size. The higher prevalence of nitrofuran metabolites in the shellfish sampled in 2011 is consistent with the beginning of frequent detection of veterinary drug residues in food of animal origin during a similar period in Taiwan [12]. For shellfish, data on the monitoring of nitrofurans and their metabolite residues is scarce. However, the TFDA surveys revealed that the most frequently observed residue (out of seven samples) was AOZ, this is similar to evidence from other reports regarding the detection of this substance in fish and shrimps [30-32]. Thus, illegal or accidental contamination with nitrofurans on farms can still occur and requires persistent and efficient monitoring **(Table 1)**.

**Table 1** The detection ration and level of banned veterinary drugs in shellfish samples collected from Taiwan between 2010 and 2015.

| Targets detected | Shellfish | Years | No. of violated samples | Violated ration (%) | Detected residues (ng/g) (ng/g) | References |
|---|---|---|---|---|---|---|
| Chloramphenicol | Hard clam | 2012 | 1 | 3.9 | 3.8 | Chang et al. [4] |
| AOZ | Hard clam | 2011 | 5 | 12.8 | 2.9-27.7 | Fu et al. [12] |
| AOZ, SEM | Sea ear | 2012 | 1 | 2.6 | 14.9 (AOZ), 4.1 (SEM) | Fu et al. [13] |
| AOZ | Sea ear | 2013 | 1 | 1.8 | 2.0 | Fu et al. [14] |

## Conclusion

Veterinary drug residues have mainly been found in food samples of animal origin that contained aquatic species known to be frequently farmed. This study documented the current violated ratios of banned veterinary drugs in shellfish products in Taiwan and the contamination levels of detected residues, to address growing concerns over the food safety of Taiwanese aquatic products. From the data available, it is concluded that chloramphenicol and nitrofurans continue to be used as growth promoters and prophylactic agents in aquatic products because of their affordability and effectiveness. However, the chloramphenicol and nitrofuran metabolite residues detected were trace amounts, only a concentration of 1 μg/kg or higher triggers TFDA enforcement action (product withdrawal and issuance of alert notifications). The results of the surveys reviewed herein indicate that the Taiwanese population is exposed to trace amounts of banned veterinary drugs with no immediate risk to consumer health through the consumption of certain hard clams and sea ears. Therefore, Taiwan's regulatory authorities and producers are required to continually monitor aquatic products and eliminate contamination sources to ensure the chemical safety of foods available to the consumer.

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