BIOACCUMULATION OF OXYTETRACYCLINE IN AQUATIC ORGANISMS AND FARM ANIMALS AND ITS RISK ON HUMAN HEALTH

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ABSTRACT:

Background: A widely use of Oxytetracycline (OTC) in aquaculture and animal farming leads to its distribution in soil, sediment and surface water. Animals in the ecosystem as well as those farm animals would accumulate the OTC from their environments with different concentrations depend upon their species and consumption behavior. Review of various bioaccumulation studies showed that OTC was accumulated in aquatic organisms and farm animals at low concentrations, but still exceeded the maximum residue limits (MRLs).

Methods: The purpose of this article was to review the OTC bioaccumulations in aquatic organisms and farm animals and assess their risks on human health. In order to assess the risk, the OTC residue concentrations found in aquatic organisms and farm animals were employed to calculate the daily intake rate and determine the risk on human health in term of Hazard Quotient (HQ). The HQ < 1 was considered to be health hazard.

Results: The HQ values less than 1 were for the consumption of aquatic species: fish (HQ <0.2), shrimp (HQ <0.09), crab (HQ <0.02) and mussel (HQ <0.05). This indicated the low risk on human health. For pork and chicken consumption, the HQ values were quite high at approximately 0.6 due to their high contamination and high consumption rate.

Conclusion: The risks with consumption of meat products were higher than with consumption of fish and shellfish. However, the data on OTC residues in these foods were limited, leading to uncertainty in the risk assessment. Further studies and additional data are recommended to confirm the risk on human health.

Keywords: Oxytetracycline, Bioaccumulation, Risk assessment, Human risk, Human health, Hazard quotient

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INTRODUCTION

Oxytetracycline (OTC) [1] [Figure 1] is a natural metabolic product of a bacterium, *Streptomyces rimosus* (Family Streptomycetaceae). In many countries, it is used as human therapeutic drug as well as antibiotic and growth promoter for livestock production. The use of swine and chicken manure as compost caused the OTC contamination in soil [2] while the effluent of animal farm [3] and aquaculture [4] were reported to be the sources of OTC in the natural water way. Although, it appeared in the environment at relatively low concentrations, Halling-Sørensen [5] suggested that OTC had potential to harm microorganisms in soil and sediment and may induce tolerance effect to human pathogen.

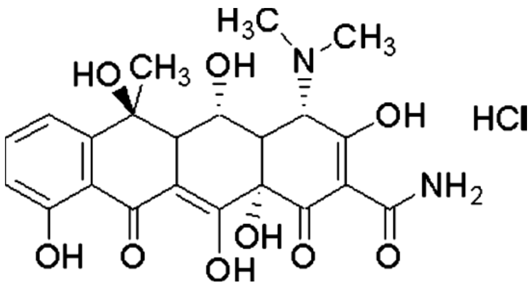

Figure 1 Chemical structure of OTC
Source: Scifinder database [1]

The toxicity of OTC to other living organisms-varies by the species. In lower trophic levels e.g. algae and aquatic plant, there are more sensitive than the species in higher trophic levels. Moreover, the toxicity would be different such as OTC affected algae and other bacteria by decreasing their

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population numbers, while it could cause death to invertebrate and fish.

Degradation of OTC is one factor that reduces its concentration in soil, water and sediment, hence decrease its bioavailability and toxicity to the organism. Lunestad and Goksryr [6] reported that the OTC sorbed on solid particle degraded slower than the OTC in aqueous phase. Under normal condition, the half-life of OTC in natural surface water at pH 7- 9, temperature between 25 -30OC with sunlight exposure is between 2.7-6.5 days [7].

Besides the degradation process, the bioavailability of OTC in the environment is under the influence of the environmental pH and its chelation with divalent metal ion. Since OTC has three dissociation constants (pK_a = 3.3, 7.3, 9.1) [8], Khanvikar et al. [9] suggested that OTC in the zwitterions form (at pH 3.6-9) could passively cross membranes faster than the polar or ionized form. As a result, the OTC absorption of the aquatic organisms in natural water (pH = 5.5-8.5) is higher. For farm animals such as chicken or swine, the pH in their small intestine is about 5-8. Therefore, pH in the gastrointestinal tract also affects their OTC absorption.

Another important property of OTC is its ability to chelate with divalent metal ions, e.g. copper (Cu^2+), magnesium (Mg^2+), and calcium (Ca^2+) [8]. These metal ions are normally added in animal feeds to improve animal health and produces quality. Nichols et al. [10] suggested that these metal ions may decrease the OTC absorptions in most organisms and result to increase the amount of OTC to be excreted. In this circumstance, either sorbed on fecal waste or suspended in the effluent, OTC has potential to re-enter the ecosystem.

Bioaccumulation of OTC in aquatic organisms

The factor that affects chemical bioaccumulation is its persistence in the living organism. Once OTC is inside, it can be accumulated or biotransformed. However, the bioaccumulations of OTC in each aquatic species were different as shown by the bioconcentration factor (BCF; L kg^{-1}) that varied from less than 2 for a bivalve [11] to more than 450 for the bryophyte [12].

In the bioaccumulation experiments with therapeutic dose, the bioaccumulation from medicated orally was approximately seven times higher than those medicated through bath [13, 14]. This indicated that fish may accumulate OTC from contaminated food more than from water. In addition, the studies also showed that OTC could accumulate in various organs especially in liver and kidney [15].

The bioaccumulation of OTC in the natural aquatic ecosystem could be different from those conducted in the laboratory due to the lower exposed concentrations with longer exposure time. In natural aquatic system, the available concentration for bioaccumulation depends on how fast the compound is degraded and how much the compound is sorbed in the sediment. Therefore, the bioavailability of OTC for the aquatic organism will vary with the environmental conditions and the consumption behaviors of each aquatic species.

Bioaccumulation of OTC in farm animals

The bioaccumulations of OTC in farm animals such as chicken, swine and cow were higher than that found in aquatic species. This probably because they uptake OTC directly from their feed while aquatic species obtained OTC from their environment. In addition, OTC could also accumulate in various organs of the animals, e.g. the residues of OTC in cow muscle, kidney and liver were 0.052, 0.373 and 1.198 mg kg^{-1} respectively [16].

Effect on human health

The ingestion of OTC contaminated food could pose the potential risk to human health. Varieties of toxic and irritation effects in humans have been reported ranges from minor effects such as sore throat, nausea and diarrhea to serious illness such as peripheral blood and liver injury [17]. World Health Organization [17] has set the allowable daily intake (ADI) for human consumption of OTC contaminated food as 0.003 mg kg^{-1} bw. Additionally, the European Union also set the maximum residue limits (MRLs) for OTC in aquatic species to protect consumer health. The MRLs (expressed as the sum of the parent drug and its 4-epimer) of OTC in muscle is 0.1 mg kg^{-1}, 0.3 mg kg^{-1} in liver, and 0.6 mg kg^{-1}in kidney [18]. In Japan and the USA, the MRL is set at 0.2 mg kg^{-1}[18].

At present, oxytetracycline is widely distributed in the environment and posed the potential risk to human health. This article aimed to review the bioaccumulation of OTC in various organisms used as food and assessed its risk on human health. In worst case scenario, the concentrations used for risk calculations were the highest residue concentration for each organism found in the reports.

MATERIALS AND METHODS

The bioaccumulations of OTC found in various organisms used as food are reviewed from the literatures and the residue concentrations in those organisms were employed to calculate OTC daily intake (I) by Environmental Protection Agency (EPA) [19]

Table 1 Residue concentrations of OTC in various aquatic species together with the corresponding calculated risk assessment on human health

Species	Reported concentrations (mg kg^{-1})	Average daily intake ($*10^{-3}$ mg kg^{-1}BW)	Risk assessment (HQ)[3]	References
Trout	1.8	0.50	0.17	[29]
Catfish	0.014 - 0.026	<0.007	<0.002	[30]
Snakehead	0.011 - 0.020	<0.006	<0.002	[30]
Tilapia	0.011 - 0.029	<0.008	<0.003	[30]
Carp	0.011 - 0.035	<0.010	<0.003	[30]
African catfish	0.26 - 0.39	0.072-0.109	0.024 -0.036	[31]
Oysters				
Crassostrea gigas	0.1	0.009	<0.003	[32]
Crassostrea magestu				
Red rock crab	0.8-3.8	0.01-0.06	< 0.02	[32]
Blue mussel	0.1-1.83	0.05-0.1	<0.05	[15]
Shrimp				
Kuruma	2.2 -2.4	0.16-0.17	<0.06	[33]
Vannamei	1.7 - 3.6	0.1-0.3	<0.09	[33]
Prawn				
Giant fresh-water prawn	0.2 -1.4	0.02 – 0.1	<0.03	[22]
Banana prawn	0 - 0.2	0.02	<0.005	[22]
Giant black-tiger prawn	0.2 -1.2	0.02-0.09	<0.03	[22]
Beef	0.05-0.14	0.05-0.15	0.02-0.05	[16]
Chicken	1.05-1.16	1.8-2	0.6-0.7	[23]
Pork	1.74	1.6	0.54	[24]

Note that reported residue concentrations obtained from the references in parenthesis

$$\text{Average Daily Intake (I)}=\frac{[C*\alpha*CR*EF*ED]}{[BW*AT]}$$

where C = OTC concentrations in organisms used as food (pork, chicken, beef, fish and shellfish)
α = absorption rate
EF = exposure frequency
ED = duration of exposure
BW = adult body weight
AT = averaged exposure time period
IR = ingestion rate for human consumption

Then, risk in term of Hazard Quotient (HQ) is calculated from HQ = I/ADI [20] where I is average daily intakes and ADI is the acceptable daily intake ($3*10^{-3}$ mg $kg^{-1}d^{-1}$) [17].

RESULTS

Bioaccumulations of OTC in various animals

0xytetracycline is approved for use in treating diseases in cattle, swine, chickens and aquaculture but lack of proper application and handling lead to its accumulation in foods of those animal origins particularly in their muscle tissue. For fish, it could obtain OTC directly from water as well as from ingestion of the contaminated aquatic organisms [21]. The accumulation of OTC in various fish species would depend upon their food consumption rates and behaviors. However, the accumulations of OTC in most fish were not much different at about 0.01-0.03 mg kg^{-1} (Table 1).

For benthic invertebrates, the different feeding behaviors allow them to expose to either dissolve or sediment bound OTC. Most benthic organisms used as human food such as mollusk, shrimp, crab, mussels would accumulate OTC from sediment [21]. However, there were some differences in bioaccumulation among the sediment feeding species as well. Le Bris et al. [11] found that the OTC bioaccumulation in Pacific oyster (*Crassostrea gigas*), short-necked clam (*Ruditapes philippinarum* and *Scrobicularia plana*) were different and might relate to their filtering rates and feeding behaviors. Table 1 showed that the OTC accumulation in benthic organisms were quite different even in the same species. For example the concentrations of OTC found in giant black tiger prawn were varied from 0.2 to1.2 mg kg^{-1} [22].

For farm animal, the OTC concentrations found in red meat samples (chicken, beef and pork) showed that the residues in chicken meat and pork were quite high (> 1 mg kg^{-1}) [23, 24] and about 10 fold higher than those found in beef sample [16] (Table 1). This probably because OTC is normally added to swine and chicken feed [13].

When the OTC concentrations found in those organisms were compared to the MRLs, the residue concentrations in pork and chicken and some benthic species were exceeded the MRLs (Table 1).

Human risk

According to US.EPA guideline [19], the average daily intake of OTC ingestion was calculated:

$$\text{Average Daily Intake} = \frac{[C*\alpha*CR*EF*ED]}{[BW*AT]}$$

where C = concentration in red meat, fish and shellfish (Table 1)

EF = exposure frequency of 350 d y^{-1} [20]

ED = duration of exposure is 70 y [20]

BW = adult body weight of 60 kg [25]

The average exposure time period (AT) for non-cancer is 70 y*365 d y^{-1}.

The IR (ingestion rate for human consumption) for fish was 0.0175 kg day^{-1} [25] and 0.0009 kg day^{-1} for crabmeat [26]. For mollusks and mussel, IR was 0.0055 kg day^{-1} and 0.0046 kg day^{-1} for shrimp [27]. Beef, pork and chicken meat were consumed 0.065, 0.058 and 0.108 kg day^{-1}, respectively [28]. The ingestion rates obtained from the reports may be varied with geological areas.

The highest concentrations of OTC found in each organisms obtained from the reports were employed to calculate the average daily intake rates for human consumption of OTC contaminated foods. The results of the calculation (Table 1) showed that the daily intakes were not exceeded the standard set by WHO (0.003 mg kg^{-1} bw d^{-1}). For fish consumptions, the daily intakes were very low (<0.00001 mg kg^{-1} bw d^{-1}) while the intakes of chicken and pork were much higher (0.001- 0.002 mg kg^{-1} bw d^{-1}). It was noted that the intake rates obtained from the consumption of any benthic species were relatively similar and in between 0.00001-0.0001 mg kg^{-1} bw d^{-1}. Comparison of the intake rates, human may expose to OTC from red meat consumption > benthic species > fish about 10-20 fold and 100 fold, respectively (Table 1).

The intake rates for the consumptions of those organisms were taken to calculate hazard quotient (HQ). The results showed that all had HQ values lower than 1. This indicated no risk on human health.

DISCUSSION

Our result revealed that the OTC residues in red meat (pork & chicken) > the sediment feeding benthic > fish. This finding could be explained by the fact that the farm animals (swine and chicken) were directly ingested OTC from the contaminated foods while the benthic obtained OTC from the sediment and fish mainly got OTC from suspended organic matter or from water. As mentioned earlier, the OTC was likely to accumulate in sediment higher than dissolved in water hence its bioavailability in sediment was higher. Furthermore, the degradation of OTC in the sediment was slower while the xenobiotic metabolism in the sediment feeding benthic was low. This was why the higher residue concentrations in the benthic species were found.

The results of the calculated-intake rates showed that the intake rates were not exceeded 0.003 mg kg^{-1} which meant that the OTC consumptions would not affect the digestive microflora [17]. Consequently, the calculation of Hazard Quotient (HQ) for all food consumptions also showed the values of less than 1. Especially, very low HQ values for the consumptions of aquatic organisms meant no direct detrimental effects from ingestion of these contaminated aquatic species. In contrast to red meat consumptions, the HQ values were quite high but lower than 1. Comparison of these HQ values to those of aquatic species, risks of red meat consumption were much higher. This is because the consumption rates and the contaminations of OTC in pork and chicken were much higher. This risk assessment suggested that a proper application and handling of any farm products to decrease the contamination in animal is needed.

Although, the results obtained from the average daily intake and HQ values were not high enough to affect human health, it was noted that the concentration in several species had exceeded the MRLs. At present, the effect of contaminated food is not directly seen, but it may cause some health effect later on. Several studies had reported on the development of OTC resistance microorganism and also the transference of the resistance gene to human pathogen [34]. In additions, the assessment on human risk was based only on reviewing of available studies and experimental data. Limiting available information on OTC residues in other living organisms (especially of food products) caused some uncertainty on risk assessment.

CONCLUSION

Oxytetracycline contaminated in soil, sediment and surface water came from animal farm and aquaculture. The OTC contamination in the environment led to its bioaccumulation in plants and animals. The extent of the bioaccumulation depended on environmental conditions, e.g. water temperature, pH, divalent cation and consumption behaviors of each species. Although, the OTC residues in most organisms were found to be at low concentration, some of them still exceeded the maximum residue limits (MRLs). The assessment indicated that consuming contaminated pork and chicken have potential hazard on human health. Human gastrointestinal microflora might be at risk if contaminated food was regularly consumed. Further studies and additional data are recommended to confirm the risk on human health.

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