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Antibacterial drugs in products originating from aquaculture: assessing the risks to public welfare

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Abstract

As aquaculture expands to meet human demand and compensate for pessimistic forecasts of fisheries catches, use of antibacterial agents to combat or forestall bacterial diseases is still a necessity, although effective vaccines and improved hygiene have aided drastically in this battle. The hazards for the consumer perspective arising from the imprudent use of such chemicals can be detrimental, especially if the residues persist above legal tolerance. These may include selection and dissemination of resistant bacteria, disruption of the colonization barrier in the human intestinal flora and allergic reactions. In cases that unlawful drugs reached the consumer via consumption of aquatic products, human health may be jeopardized even further. The present review article assesses these risks to human health.

Keywords: Aquaculture; Antibacterials; Risks; Resistance; Human welfare.

Introduction

Nowadays, aquaculture is considered to be the fastest growing food production industry, boosted by governmental and technological impulsion, thus reducing the world's dependence on fisheries and offering financial relief to developing countries, which are the main contributors to this tremendous increase (GOLDBURG & NAYLOR, 2005). In particular, aquaculture participation in global supplies of aquatic products

(fish, mollusks, crustaceans and aquatic plants) has quadrupled in comparison to its production in the 70's (38% of total fisheries production in 2004, accounting for 59.4 million tonnes and US\$ 70.3 billion; FAO, 2007). Although aquaculture initially emerged as a benign industrial sector, its accelerated growth seems on some occasions to have proceeded ahead of adequate care for environmental and public welfare, even in the face of accumulated evidence of side effects. As intensive aquaculture involves farming

where large numbers of animals are kept together in a confined space, outbreaks of disease are common, regardless of the quality of the hygiene practised. Bacterial diseases remain a major cause of mortalities and therefore a potential source of significant financial loss for the industry. Where vaccine application is not available, bacterial pathogens are dealt with by antibacterials, the administration of which is complicated due to the fact that the substances inevitably enter the aquatic environment either via the feed or directly into the water. Various registered antibacterial agents such as tetracyclines, (fluoro)quinolones, potentiated sulfa, penicillins, macrolides and amphenicols are used globally to treat bacterial outbreaks in aquatic farms (COSTELLO, 2001; SHAO, 2001). Several studies have stressed the implications of the use antibacterials in aquaculture throughout the world on human and environmental welfare (ANGULO, 2000; HAYA *et al.*, 2000; ANGULO *et al.*, 2004; BOXALL *et al.*, 2004; CABELLO, 2004; RIGOS & TROISI, 2005).

Legislation enforcing the use of chemotherapeutics varies among countries throughout the world (SERRANO, 2005). International organizations, including the Food & Agriculture Organization (FAO), the World Health Organization (WHO), the International Office of Epizootics (OIE), the Committee for Veterinary Medicinal Products (CVMP) and national agencies such as the U.S. Food and Drug Administration (FDA) have all raised issues associated with heavy use of antibacterials in all animal production sectors, with particular concern for potential risks to public health. Guidelines such as the acceptable daily intake (ADI), maximum residue levels (MRL) and withdrawal times have been established to protect the consumer from side effects.

Unfortunately, antibacterial drugs have not always been used in a responsible manner to confront bacterial diseases. The urgency of the farmer's response to an outbreak, often results in ill-informed decision-making based on a rushed diagnosis and possible use of inappropriate drugs and dosing regimens. Thus, the marketing of aquatic products with residual drugs above the legal tolerance level, occasionally containing even banned substances, (chloramphenicol, nitrofurans) is not uncommon (WILLIS *et al.*, 1999; JOHNSTON & SANTILLO, 2002; PUBLIC CITIZEN, 2004; FOOD AND WATER WATCH, 2007). Although it is generally accepted that the use of antibacterials follows a decreasing pattern in relation to aquaculture production growth, antibacterial therapy has been challenged by specialist groups such as environmentalists and public health experts on the basis that it may threaten human welfare by inducing: a) development and transfer of bacterial resistance b) accidental contamination of the consumer with antibacterial residues, possibly affecting human intestinal flora c) toxic effects resulting from the consumption of unlawful substances and d) emergence of allergic reactions.

Development and dissemination of bacterial resistance

Development of bacterial resistance as a result of antibacterial use is of high concern in all culture environments and has raised considerable debate in human and veterinary medicine, including aquaculture (SMITH *et al.*, 1994; ALDERMAN & HASTINGS, 1998; ANGULO, 1999; SORUM, 1999; ANGULO, 2000; ANDERSON *et al.*, 2003; ANGULO, 2004; CABELLO, 2004; 2006). Several important fish pathogens have revealed their abil-

ity to develop resistance as a consequence of antibacterial exposure including *Aeromonas salmonicida*, *A. hydrophila*, *Edwardsiella tarda*, *Yersinia ruckeri*, *Photobacterium damselae subsp. piscicida*, *Vibrio anguillarum*, *V. salmonicida*, *P. psychrophilum* and *Pseudomonas fluorescens* (SERRANO, 2005; SORUM, 2006).

Nowadays, transfer of antibacterial resistance between veterinary and human medicine has become a global issue and has stimulated intense criticism (SMITH *et al.*, 1994; ALDERMAN & HASTINGS, 1998; ANGULO *et al.*, 2004). It is unfortunate that antibacterials commonly used for veterinary purposes, including aquaculture therapy (eg. quinolones, tetracyclines and potentiated sulfa), are also employed in human medicine (SERRANO, 2005). Inevitably, the use of antibacterials in the aquaculture industry can favour the occurrence of antibacterial resistance in another therapeutic field, such as human medicine. It has been indicated that dissemination of antibacterial resistance may be facilitated by the horizontal transfer of R plasmids between related and diverse bacteria (WATANABE *et al.*, 1977; AOKI, 1988). These resistance genes have no phylogenetic, geographical or ecological barriers (OIE/FAO/WHO, 2004). Thus, fish pathogens which may have developed acquired resistance as a result of drug usage and the continuous presence of residual levels in the fish body, can act as a host for resistance genes that can be transferred to human pathogens (e.g. the spread of a resistance gene from *Aeromonas* spp. to *E. coli* and the resistance acquisition of *V. cholerae* and *Vibrio parahaemolyticus*; ANGULO, 1999), even moving from one producing country to another (OIE/FAO/WHO, 2004). This is considered as an indirect transfer of resistance from aquaculture to

human medicine caused by horizontal gene transfer and has been demonstrated also *in vitro*. For example, plasmids carrying resistance determinants have also been transferred from fish to human pathogens including *V. cholerae* (AOKI, 1988), *V. parahaemolyticus* (NAKJIMA *et al.*, 1983) and *E. coli* (SON *et al.*, 1997).

Moreover, the use of antibacterial drugs in aquaculture may also select for resistance bacteria that are not fish pathogens, which is regarded as a direct pathway of resistance from aquatic practices to humans. Bacterial pathogens resistant to drugs have been isolated from the intestinal contents of farmed and wild fish species captured around fish farms (ERVIK *et al.*, 1994). This indicates that wild inhabitants of farming sites subjected to medication can also act as a reservoir of resistance dissemination. Antibacterial resistant bacteria may be transmitted to humans when the aquacultured products (primary or secondary) are improperly cooked and eaten (eg. *Aeromonas* spp, *Edwardsiella tarda*, *E. coli*, *Plesiomonas shigelloides*, *Salmonella* spp., *Shigella* spp., *V. cholerae*, *V. parahaemolyticus*, and *V. vulnificus*) (IASR, 1999; WHO, 1999).

Residual antibacterials in aquatic farmed items; possible effects on human intestinal microflora

The possible presence of residual antibacterials in commercialized farmed aquatic products and the associated risks to the consumer has been the subject of several investigations (GOLDBURG *et al.*, 2001; JOHNSTON & SANTILLO, 2002; CABELLO 2003; 2004; ANGULO *et al.*, 2004; HASTEIN *et al.*, 2006). Another hidden threat from drug pollution from aquatic farms is the potential accumulation of drug residues in the aquatic food chain

(from uneaten medicated feed, fish excretions, baths) leading to direct or indirect exposure of biota around farm sites. Secondary farmed items including scavengers and wild-caught fish destined for human consumption and harvested from areas around farm sites, have been found to be contaminated with antibacterial drugs to levels beyond the safety factor (BJORKLUND *et al.*, 1990; 1991; SAMUELSEN *et al.*, 1992; ERVIK *et al.*, 1994; CAPONE *et al.*, 1996; COYNE *et al.*, 1997). In these studies, drug concentrations (oxolinic acid, flumequine, oxytetracycline) ranging from 0.1 to 12.5 µg/g tissue were measured in wild fauna (mussels, crabs, fish) inhabiting the adjacent areas of farming sites subjected to medication.

The risks of antibacterial residues to human welfare, with particular reference to intestinal microflora, have been stressed by several authorities (FDA, 1993; CVMP, 1995). Although residual drugs may be degraded by cooking procedures to some degree (XU *et al.*, 1996; UNO *et al.*, 2006) and inactivated to a variable extent in the intestines by decomposition of bacterial enzymes and by binding to bacteria and other faecal components, the possibility of inducing alteration of the intestinal flora and disruption of the colonization barrier is not unlikely (VAN DER WAAIJ, 1982; EDLUND & NORD, 1993; VOLLARD & CLASENER, 1994; CERNIGLIA & KOTARSKI, 1999; EDLUND & NORD, 1999). Human intestinal microflora constitute a balanced and complex community inhabited by hundreds of bacterial species (CERNIGLIA & KOTARSKI, 1999) which are vital for the maintenance of a healthy human gastrointestinal tract since they inhibit colonization of pathogenic bacteria (VOLLARD & CLASENER, 1994) and intervene in the digestion and processing

of various substances (CHADWICK *et al.*, 1992). Although the side effects of drugs on human intestinal microflora can be more apparent during therapeutic applications where the tissue levels to be targeted are high, however, prolonged unwanted exposure to antibacterial residues may also disturb the equilibrium of the gut microflora by changing the population density and composition (antibacterials may reduce total numbers of some bacteria or selectively kill some vital species), by altering enzyme activity for the metabolism of endogenous and exogenous substances and by impairing colonization resistance (CERNIGLIA & KOTARSKI, 1999). This may have serious consequences for the consumer, including increased susceptibility to infection by exogenous potential bacterial pathogens (eg. *Salmonella* sp.), favouring the colonization of new resistant pathogenic bacteria and the outgrowth of indigenous opportunistic inhabitants which may be part of the normal flora (eg. *Escherichia coli* and yeasts) (TANCREDE, 1992; GORBACH, 1995; NORD & EDLUND, 1991; VOLLARD & CLASENER, 1994; CABELLO, 2004).

Residual unlawful antibacterials

During the last decade, the detection of illicit antibacterials (chloramphenicol and nitrofurans) in aquaculture products has not been an uncommon issue (FOOD STANDARDS AUSTRALIAN NEW ZEALAND, 2004; PUBLIC CITIZEN, 2004; FOOD AND WATER WATCH, 2007). The detection of chloramphenicol and nitrofurans residues in exported Asian aquatic farmed products, has alarmed national and international authorities, resulting occasionally in a slowdown or shutdown of imports in the consuming coun-

tries, thus causing financial loss in the producing countries and reducing the credibility of the aquaculture industry at a global level (PUBLIC CITIZEN, 2004; FOOD AND WATER WATCH, 2007). The initiation of these episodes took place during 2001-2002 when EU food authorities detected unacceptable levels of chloramphenicol and nitrofurans in imported shrimp from several Asian countries (China, Vietnam, Indonesia, Thailand and India; PUBLIC CITIZEN, 2004). During the same period, the discovery of chloramphenicol levels in crawfish and shrimp (China, Vietnam) was also the case in several states in the USA (MCGOVERN, 2002; SEAFOOD, 2002;). FOOD STANDARDS AUSTRALIAN NEW ZEALAND (2004) reported that imported prawns were contaminated with nitrofurans (mainly represented by furazolidone; a commonly used illegal nitro-furan) during the production cycle.

Chloramphenicol can be used only as a therapeutic last resort in life-threatening cases in human medicine (for typhoid fever and meningitis when no other drugs are available, and for conjunctivitis). The substance is highly toxic and potentially fatal for humans even at trace levels. Therefore, national authorities and international organizations have established zero tolerance, indicating no acceptability of detectable residues in food products (PUBLIC CITIZEN, 2004). Evaluations performed by GESAMP (1997) stressed that the compound is capable of producing genetic damage, allergies, anemia and cancer. Moreover, the drug may cause aplastic anemia, an irreversible condition affecting bone marrow causing it to stop producing red and white blood cells (YOUNG & KAUFMAN, 2008). Nitrofurans are also very dangerous for human health due to their potential carcinogenic properties

(WHO, 1993). It was also stressed by the same review meeting that furazolidone induced a variety of tumours in mice and rats and was positive in *in vitro* genotoxicity tests.

Chloramphenicol and nitrofurans are also banned in the respective producer countries, however the non-compliance of particular farmers with these guidelines may have caused uncontrolled contamination of local consumers with illicit substances when the treated aquatic products reached the local markets. The lack of an immediate response to these issues in the importing countries and/or the employment of insensitive analytical methods during the inspection procedure may indicate that hazardous unlawful drugs may have already been consumed via imported aquaculture products with unknown consequences.

Allergic reactions

Accidental consumption of antibacterial agents in aquacultured products can generate allergies in sensitive consumers. Such cases, however, are of lesser concern, are also difficult to monitor and consequently are underestimated.

Conclusion

At least for the immediate future, antibacterials should be the last resort when dealing with bacterial outbreaks in aquaculture practices, regardless of the improvement of disease management and vaccine development. Use of antibacterials especially in developing countries may jeopardise human health if inappropriate drug selection, treatment schedules and safety guidelines are considered. Given that antibacterial resistance is a serious global issue with obvious, devastating consequences on human health, it is mandatory that ther-

apy in the rapidly developing aquaculture sector receives special additional attention from federal agencies in order to eliminate its contribution to this crisis. Residues of banned substances in aquacultured products originating from the Orient are also of significant concern and thus an increased inspection effort from authorities of both producing and importing countries must be applied to increase protection of consumers.

Alternative preventive and therapeutic methods must be seriously considered to reduce the use of drugs.

References

- ALDERMAN, D.J. & HASTINGS, T.S., 1998. Antibiotic use in aquaculture: development of antibiotic resistance-potential for consumer health risks. *International Journal of Food Science and Technology*, 33 (2): 139-155.
- ANDERSON, A.D., MCCLELLAN, J., ROSSITER, S. & ANGULO, F.J., 2003. Public health consequences of use of antimicrobial agents in agriculture. p. 231-243. In: *The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment*. Workshop Summary, Washington, D.C., National Academies Press.
- ANGULO, F., 1999. Use of antimicrobial agents in aquaculture: potential for public health impact. Public Health Service. Atlanta: Department of Health & Human Services, Centers for Disease Control and Prevention. (18 October 1999). Available at: <http://www.fda.gov/ohrms/dockets/dailys/00/apr00/041100/c000019.pdf>.
- ANGULO, F., 2000. Antimicrobial agents in aquaculture: potential impact on health. *APUA Newsletter*, 18: 1-6.
- ANGULO, F.J., NARGUND, V.N. & CHILLER, T.C., 2004. Evidence of an association between use of antimicrobial agents in food animals and antimicrobial resistance and health consequences of such resistance. *Journal of Veterinary Medicine*, 51 (8-9): 374-379.
- AOKI, T., 1988. Drug resistant plasmids from fish pathogens. *Microbiological Sciences*, 5: 219-223.
- BJORKLUND, H., BONDESTAM, J. & BYLUND, G., 1990. Residues of oxytetracycline in wild fish and sediments from fish farms. *Aquaculture*, 86: 359-367.
- BJORKLUND, H., RABERGH, C.M.I. & BYLUND, G., 1991. Residues of oxolinic acid and oxytetracycline in fish and sediments from fish farms. *Aquaculture*, 97: 85-96.
- BOXALL, A.B., FOGG, L.A., BLACKWELL, P.A., KAY, P., PEMBERTON, E.J. & CROXFORD, A., 2004. Veterinary medicines in the environment. *Reviews of Environmental Contamination and Toxicology*, 180: 1-91.
- CABELLO, F.C., 2003. Antibiotics and aquaculture. An analysis of their potential impact upon the environment, human and animal health in Chile. Fundacion Terram. *Analisis de Politicas Publicas*, (17): 1-16. http://www.terram.cl/docs/App17_Antibioticos_y_Acui-cultura.pdf
- CABELLO, F.C., 2004. Antibiotics and aquaculture in Chile: implications for human and animal health. *Revista Medica de Chile*, 132: 1001-1006.
- CABELLO, F.C., 2006. Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. *Environmental Microbiology*, 8: 1137-1144.
- CAPONE, D.G., WESTON, D.P., MILLER,

- V. & SHOEMAKER, C., 1996. Antibacterial residues in marine sediments and invertebrates following chemotherapy in aquaculture. *Aquaculture*, 145 (1-4): 55-75.
- CERNIGLIA, C.E. & KOTARSKI, S., 1999. Evaluation of Veterinary Drug Residues in Food for Their Potential to Affect Human Intestinal Microflora. *Regulatory Toxicology and Pharmacology*, 29 (3): 238-261.
- CHADWICK, R.W., GEORGE, S.E. & CLAXTON, L.R., 1992. Role of gastrointestinal mucosa and microflora in the bioactivation of dietary and environmental mutagens or carcinogens. *Drug Metabolism Reviews*, 24 (4): 425-492.
- COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS (CVMP), 1995. *Safety evaluation of antimicrobial substances regarding the effects on human gut flora*. Committee for Veterinary Medicinal Products Working Party on the Safety of Residues, Brussels, Belgium. [Guideline Document No. III/5619/94-EN].
- COSTELLO, M.J., GRANT, A., DAVIES, I.M., CECCHINI, S., PAPOUTSO-GLOU, S., QUINGLEY, D. & SAROGLIA, M., 2001. The control of chemicals used in aquaculture in Europe. *Journal of Applied Ichthyology*, 17: 173-180.
- COYNE, R., HINEY, M. & SMITH, P., 1997. Transient presence of oxytetracycline in mussels (*Mytilus edulis*) following its therapeutic use at a marine Atlantic salmon farm. *Aquaculture*, 149 (3-4): 175-181.
- EDLUND, C. & NORD, C.E., 1993. Ecological impact of antimicrobial agents on human intestinal microflora. *Alpe Adria Microbiology Journal*, 3: 137-164.
- EDLUND, C. & NORD, C.E., 1999. Effects of quinolones on intestinal ecology. *Drugs*, 58 (Suppl. 2): 65-70.
- ERVIK, A., THORSEN, B., ERIKSEN, V., LUNESTAD, B.T. & SAMUELSEN, O.B., 1994. Impact of administering antibacterial agents on wild fish and blue mussels *Mytilus edulis* in the vicinity of fish farms. *Diseases of Aquatic Organisms*, 18: 45-51.
- FAO, 2007. The state of world fisheries and aquaculture 2006. Part 1: World review of fisheries and aquaculture. Rome, FAO, 162 pp.
- FDA: U.S. FOOD AND DRUG ADMINISTRATION, 1993. *Proposed Guideline: Microbiological Testing of Antimicrobial Drug Residues in Food*. FDA, Rockville, MD. December 2-16.
- FOOD STANDARDS AUSTRALIA NEW ZEALAND, 2004. Nitrofurans in prawns. A Toxicological Review and Risk Assessment. *Technical report series* No. 31, November 2004.
- FOOD & WATER WATCH, 2007. Import alert. Government fails Consumers, Falls Short on Seafood Inspections. 1400 16th St. NW, Suite 225. www.foodand-waterwatch.org.
- GESAMP, 1997. Towards safe and effective use of chemicals in coastal aquaculture. *Reports and Studies, GESAMP*. No. 65. FAO, Rome, 40 pp.
- GOLDBURG, R. & NAYLOR, R., 2005. Future seascapes, fishing, and fish farming. *Frontiers in the Ecology and the Environment*, 3 (1): 21-28.
- GOLDBURG, R.J., ELLIOTT, M.S. & NAYLOR, R.L., 2001. *Marine Aquaculture in the United States: Environmental Impacts and Policy Options*. PEW Oceans Commission, Arlington, Virginia.
- GORBACH, S. L., 1995. Perturbation of intestinal microflora. *Veterinary and Human Toxicology*, 35 (Suppl. 1): 15-23.

- HASTEIN, T., HJELTNES, B., LILLEHAUG, A., UTNE SKARE, J., BERTSEN, M. & LUNDEBYE, A.K., 2006. Food safety hazards that occur during the production stage: challenges for fish farming and the fishing industry. *Revue Scientifique et Technique, Office International des Epizooties*, 25 (2): 607-625.
- HAYA, K., BURRIDGE, L.E. & CHANG, B.D., 2000. Environmental impact of chemical wastes produced by the salmon aquaculture industry. *ICES Journal of Marine Science*, 58: 492-496.
- JOHNSTON, P. & SANTILLO, D., 2002. *Chemical Usage in Aquaculture: Implications for Residues in Market Products*. Greenpeace Research Laboratories Technical Note 06/2002: 15 pp.
- MCGOVERN, D., 2002. First U.S. case of chloramphenicol found in Chinese crawfish. Worldcatch News Network. May 6, 2002.
- IASR, 1999. *Vibrio parahaemolyticus*, Japan, 1996-1998. *IASR Infectious Agents Surveillance Report*, 20: 159-160.
- NAKJIMA, T., SUZUKI, M., HARADA, K., INOUE, M. & MITSUHASHI, S., 1983. Transmission of R plasmids in *Vibrio anguillarum* to *Vibrio cholerae*. *Microbiology Immunology*, 27 (2): 195-198.
- NORD, C.E. & EDLUND, C., 1991. Ecological effects of antimicrobial agents on the human intestinal flora. *Microbial Ecology in Health and Diseases*, 4 (4): 193-207.
- OIE/FAO/WHO, 2004. *Joint FAO/OIE/WHO 1st Expert workshop on non-human antimicrobial usage and antimicrobial resistance: scientific assessment*. Geneva, Switzerland, 1-5 December 2003. <http://www.who.int/foodsafety/publications/micro/en/>
- PUBLIC CITIZEN, 2004. CHEMICAL COCKTAIL. The Health Impacts of Eating Farm-Raised Shrimp. A special report by Public Citizen's Food Program. Public citizen Pennsylvania Ave SE, Washington D.
- RIGOS, G. & TROISI, G., 2005. Antibacterial agents in Mediterranean finfish farming: a synopsis of drug pharmacokinetics in important euryhaline fish species and possible environmental implications. *Reviews in Fish Biology and Fisheries*, 15 (1-2): 53-73.
- SAMUELSEN, O.B., LUNESTAD, B.T., HUSEVAG, B., HOLLELAND, T. & ERVIK, A., 1992. Residues of oxolinic acid in wild fauna following medication in fish farms. *Diseases of Aquatic Organisms*, 12: 111-119.
- SEAFOOD.COM., 2002. 'Shrimp hits the fan on chloramphenicol.' July 7, 2002.
- SERRANO, P.H., 2005. Responsible use of antibiotics in aquaculture. *FAO Fisheries Technical Paper*. No. 469, Rome, FAO, 97 pp.
- SHAO, Z.J., 2001. Aquaculture pharmaceuticals and biologicals: current perspectives and future possibilities. *Advanced Drug Delivery Reviews*, 50 (3): 229-243.
- SMITH, P., HINEY, M.P. & SAMUELSEN, O.B., 1994. Bacterial resistance to antimicrobial agents used in fish farming: a critical evaluation of method and meaning. *Annual Review of Fish Diseases*, 4: 273-313.
- SON, R., RUSUL, G., SAHILAH, A.M., ZAINURI, A., RAHA, A.R. & SALRNAH I., 1997. Antibiotic resistance and plasmid profile of *Aeromonas hydrophilia* isolates from cultured fish, *Tilapia (Tilapia mossambica)*. *Letters of Applied Microbiology*, 24 (6): 479-482.
- SORUM, H., 1999. Antibiotic resistance in aquaculture. *Acta Veterinaria Scandi-*

- navica*, 92 (Suppl.): 29-36.
- SORUM, H., 2006. Antimicrobial Drug Resistance in Fish Pathogens. p.213-238. In: *Antimicrobial Resistance in Bacteria of Animal origin*, edited by F. Aarestrup. ASM Press. Washington DC, USA.
- TANCREDE, C., 1992. Role of human microflora in health and disease. *European Journal of Clinical Microbiology & Infectious Diseases*, 11 (11): 1012-1015.
- UNO, K., AOKI, T., KLEECHAYA, W., TANASOMWANG, V. & RUANGPAN, L., 2006. Pharmacokinetics of oxytetracycline in black tiger shrimp, *Penaeus monodon*, and the effect of cooking on the residues. *Aquaculture*, 254 (1-4): 24-31.
- VAN DER WAAIJ, D., 1982. Colonization pattern of the digestive tract by potentially pathogenic microorganisms: Colonization controlling mechanisms and consequences for antibiotic treatment. *Infection*, 11 (Suppl. 2): 90-92.
- VOLLARD, E.J. & CLASENER, H.A.L., 1994. Colonization resistance. *Antimicrobial Agents and Chemotherapy*, 38 (3): 409-414.
- WATANABE, T.T., AOKI, Y., OGATA, Y. & EGUSA, S.R., 1977. Factors related to fish culturing. *Annals of the New York Academy of Sciences*, 182 (1): 383-410.
- WHO, 1993. Evaluation of certain veterinary drug residues in food (Fortieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO *Technical Report Series*, No. 832, 62 pp.
- WHO, 1999. Food safety issues associated with products from aquaculture: report of a joint FAO/NACA/WHO study group. *WHO Technical Report Series*, No. 883, 55 pp.
- WILLIS, C., BOOTH, H., WESTACOTT, S. & HAWTIN, P., 1999. Detection of antibacterial agents in warm water prawns. *Communicable Diseases and Public Health*, 2 (3): 210-214.
- XU, D., GRIZZLE, G.M., ROGER, W.A. & SANTERRE, C.R., 1996. Effect of cooking on residues of ormetoprim and sulfadimethoxine in the muscle of channel catfish. *Food Research International*, 29 (3-4): 339-344.
- YOUNG, N.S. & KAUFMAN, D.W., 2008. The epidemiology of acquired aplastic anemia. *Haematologica*, 93 (4): 489-492.

