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Human health aspects of drug and chemical use in aquaculture

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Abstract. This document briefly reviews the potential and, in particular, some relevant hazards associated with the use of veterinary drugs and chemicals in aquaculture. Regardless of the developments aimed at the reduction of the risk associated with these types of hazards, during the last decade a number of problems have existed in practice, as detected by the analysis of fish (local and imported) and resulting bans. The whole picture is rather complex, and risk management approaches differ from country to country. The general advice to aquaculture producers is to resort, if necessary, only to veterinary drugs and chemicals approved for the target market, utilize them according to the prescription and, in particular, follow the withdrawal time according to the treatment.

Keywords. Aquaculture – Veterinary drugs – Chemicals – Hazards – Risk.

Aspects concernant la santé humaine par rapport à l'utilisation de produits pharmaceutiques et chimiques en aquaculture

Résumé. Ce document passe brièvement en revue le potentiel et, en particulier, certains dangers liés à l'utilisation de médicaments vétérinaires et produits chimiques en aquaculture. Malgré les développements visant à la réduction du risque lié à ces types de dangers, un certain nombre de problèmes ont existé dans la pratique, lors de la dernière décennie, comme l'a détecté l'analyse du poisson (local et importé), avec les interdictions subséquentes. Il est plutôt complexe de dresser un tableau complet de la situation, étant donné que les approches de gestion de risques diffèrent d'un pays à l'autre. La recommandation générale que l'on fait aux producteurs aquacoles est de ne recourir, si nécessaire, qu'aux médicaments vétérinaires et produits chimiques approuvés pour le marché-cible, de les utiliser conformément aux prescriptions, et, en particulier, de respecter le temps d'attente correspondant au traitement.

Most-clés. Aquaculture – Médicaments vétérinaires – Produits chimiques – Dangers – Risque.

I – Introduction

Hazards in fish and fish products, including those from aquaculture, according to the FAO/WHO Codex Alimentarius Commission are: "A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect" (CAC, 1969). In the case of food hazards, adverse health effects refer to human beings. The residues of veterinary drugs and chemicals utilized in aquaculture form part of the large group of so-called "chemical hazards".

Hazards coming from the use of chemical and veterinary drugs in aquaculture are not the only hazards that could affect aquacultured fish. Perhaps hazards due to post-harvest handling (e.g. microbiological) continue, as in wild fish, to be the most important from the point of view of public health, in situations where a responsible use of chemicals and veterinary drugs and good aquaculture practices are implemented (Fairgrieve and Rust, 2003). During the last decade, some environmental hazards, like the accumulation of polychlorinated biphenyls (PCBs) and dioxins in farmed fish, have gained the attention of food risk managers (Focardi *et al.*, 2005).

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Some of the environmental pollutants could be introduced to aquacultured fish through feeds and water.

Whereas the number of potential food hazards, or *possible* hazards, could be very large, the number of *probable* (or relevant) hazards is in actual situations limited. Possible hazards are identified from human epidemiological records and scientific research studies and are usually incorporated into fish safety regulations after a risk analysis exercise. In this document, we are going to concentrate our analysis on the hazards due to the use of chemical and veterinary drugs in aquaculture.

The Codex Alimentarius definition of hazard is also the definition already incorporated conceptually into most fish safety regulations around the world, particularly since the adoption of hazard analysis and critical control point (HACCP)-based regulations. Current specific regulations at the country level concerning possible hazards in fish apply to aquacultured fish and fish products. In turn, there are regulations that point to specific hazards related to aquaculture (e.g. veterinary drug residues, feeds, quality of water for aquaculture). To identify probable hazards requires a specific hazard analysis, at least at the level of implementation of a HACCP system.

The probability of a hazard actually being present in fish and fish products from aquaculture, either at the time of slaughter or at the time the final product is consumed, depends, in turn, on a number of factors. For instance, the relevance of the hazard (risk) could vary for the same type of cultured fish due, for instance, on the one hand to the environment and the rearing system, and on the other hand to cooking and consumption patterns and the susceptibility of the consumer. The current tendency is towards a risk analysis approach, which means an approach where the risk assessment, risk management and risk communication are clearly separated and could play a role in the mitigation of the actual identified risk (Hernandez Serrano, 2005). The way risk assessments are performed in practice varies according to the type of hazard and to specific country regulatory practices. At the level of a risk analysis, the first step when analyzing a hazard-specific food combination should be the production of a "risk profile" (CAC, 2007).

Residues of chemicals and veterinary drugs that could constitute a hazard to consumers of fish and fish products from aquaculture comprise a number of substances, including substances that are authorized by regulations for use, as well as non-authorized substances (Lupin *et al.*, 2003). They are usually sub-divided into two groups:

- (i) Antibacterial substances (including sulphonamides).
- (ii) Veterinary drugs other than antibiotics.

These groups include substances that in some cases could have a maximum regulatory limit (MRL) –those approved for use– whereas others must be absent from fish and fish products. Nevertheless, at the same time, a drug could be accepted in one country and not in another.

Furthermore, the presence of chemical and drug residues in fish could be due not only to the intentional use of the specific chemical or drug, but as a result of an interaction between the cultured fish and the environment. It is well known that some drugs and chemicals biodegrade relatively soon, or do not form toxic products in the process of biodegradation, whereas others remain for a long time in the environment or produce toxic degradation products, which in turn could remain for a long time in the environment (Capone *et al.*, 1996; Srivastava *et al.*, 2004). Human use (and misuse) of medicines (chemicals and antibiotics) seems to be mainly responsible for residues in aquatic environments (Hirsch *et al.*, 1999; Yu-Chen Lin *et al.*, 2008), but polluted spots can not be discarded, particularly at points where there is large aquaculture production.

Regardless of the possible different sources for the origin and reasons for the chemical and veterinary drug residues in fish, a recent Canadian study (Tittlemier *et al.*, 2007) concerning the presence of 39 different veterinary drug residues in thirty composite samples of shrimp, marine

fish, freshwater fish and canned fish, estimated the dietary exposure of Canadians to these residues, revealing the presence of:

- (i) AOZ (a metabolite of furazolidone) (4/30 samples)
- (ii) Enrofloxacin (3/30 samples)
- (iii) Leucomalachite green (3/30 samples)
- (iv) Oxolinic acid (2/30)
- (v) AMOZ (a metabolite of furaltadone) (1/30 samples)
- (vi) Chloramphenicol (1/30 samples)
- (vi) SEM (a metabolite of nitrofurazone) (1/30)

Whereas concentrations of residues were low (in the order of ng/g) there is no doubt that Canadians were exposed, via fish and shrimp consumption, to some banned and unapproved veterinary drug residues.

The case of residues of antibacterial substances in fish and fish products (and food in general) represents, in practice, a rather complex problem for society and regulators, particularly in developing countries where regulations and the possibilities to enforce them are scarce (Cabello, 2006). In the first place, there is a balance between the need to raise healthy food animals economically and the possible impact of residues in foods on people directly or through the intermediation of the environment. Moreover, as antibiotics utilized in animal culture are the same as those utilized in human medicine, there is the question of how residues of antibiotics used directly in human medicine affect the whole picture, as well as more common aspects such as the disposal of unused or expired products (Jørgensen and Halling-Sørensen, 2000). All these questions require, in practice, a very articulated policy to protect consumers (consumers-citizens). A recent paper by Viola and DeVincent (2006) exemplifies the complexity of the manufacture, distribution and use of antimicrobials in animals in the United States.

At the international level, the United Nations Food and Agriculture Organization (FAO) adopted a Code of Conduct of Responsible Fisheries in 1995 (FAO, 1995) that included aquaculture. Furthermore, Article 9 of the Code, specific to aquaculture was analyzed and expanded in a subsidiary document (FAO, 1997). This latter document called for the global aquaculture industry to make safe and effective use of feeds, feed additives, veterinary drugs and other chemicals, and promote the use of aquaculture practices and methods which reduced hazards (in fish as human food).

FAO, WHO and the OIE have convened a number of international meetings on the subject during the last decade, including: "Food safety issues associated with products from aquaculture" (FAO/NACA/WHO, 1997); "Harmonization of National Antimicrobial Resistance Monitoring and Surveillance Programmes in Animals and Animal-Derived Foods" (OIE, 2000); "Non-human Antimicrobial Usage and Antimicrobial Resistance" (FAO/OIE/WHO, 2003); "Technical Workshop on Residues of Veterinary Drugs without ADI/MRL" (FAO/WHO, 2004) and "Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance" (FAO/OIE/WHO, 2006). FAO has also published a review document on responsible use of antimicrobials (Hernández Serrano, 2005) that could be utilized as a background document in the drafting of specific risk profiles.

Regarding the Codex Alimentarius Commission (CAC) there are a number of documents that apply to the subject, as listed in Table 1.

The texts of the CAC are general in nature; however, they apply to fish aquaculture. The number of veterinary drugs approved for aquaculture by CAC is, however, rather limited. A more specific section, related to the implementation of HACCP, can be found in Section 6 of the CAC Code of Practice for Fish and Fishery Products (CAC, 2003).

In addition to the UN concerned agencies and the CAC, concerned scientists launched a call for progress in a worldwide aquaculture drug and vaccine registration process (Schnick *et al.*,

2005), however, any actual progress in this area, at the international level, could still be considered limited.

Table 1. Codex Alimentarius Commission (CAC) documents related to the use of veterinary drugs[†]

Year	Code	Title
1993 / Amended 2003	CAC/MISC 5	Glossary of terms and definitions (Residues of Veterinary Drugs in Foods)
1993	CAC/RCP 38	Recommended International Code of Practice for control of the use of veterinary drugs
1993	CAC/GL 16	Codex Guidelines for the establishment of a regulatory programme for control of veterinary drug residues in foods
2005 2008	CAC/RCP 61 CAC	Code of Practice to minimize and contain antimicrobial resistance Maximum Residue Limits (MRL) for Veterinary Drugs in Foods. Updated at the 31st Session of the Codex Alimentarius Commission (July 2008)

[†]All the texts (English, French and Spanish) can be obtained free of charge from: http://www.codexalimentarius.net/web/standard_list.do?lang=en.

II – Antibacterial substances

As in other animal production sectors, antibacterial substances (antibiotics and sulphonamides) are utilized in aquaculture production with the purpose of prevention (prophylactic) and treatment (therapeutic use) of bacterial diseases (Lupin *et al.*, 2003). Antibiotics have also been utilized as growth factors, even if this is not now considered to be a good practice. Antibiotics utilized in aquaculture are of the same type utilized to treat bacterial diseases in humans.

Hazards of antibacterial substances utilized in aquaculture production to public health could be classified as follows:

- (i) Hazards due to the residues of approved antibiotics in fish and fish products.
- (ii) Hazards due to the residues of unapproved or banned antibiotics.

(iii) Hazards due to the development of resistance to antibiotics in microbial pathogens in the environment due to the use of antibiotics (approved or not) (Acar and Röstel, 2001).

Hazards due to residues of approved antibiotics in fish and fish products appear when residue levels in aquacultured fish are over the maximum residue levels (MRLs) established by regulations. The MRLs that exist at the national level in different countries (mainly developed countries) have been determined following agreed procedures and criteria to assess and manage the risk posed to consumers by the ingestion of such residues.

The way to accomplish this with regulations is, in this case, to utilize only approved antibiotics in the concentrations and with the purpose for which they have been approved, and to observe the proper withdrawal time period before culling in order to reduce any residues in fish below the approved MRL. In some countries, and for some species, the supply of antibiotics is stopped well before animals reach commercial size. In addition, public fish inspection services could verify the compliance with regulations by random sampling at the farm level.

Hazards due to residues of unapproved or banned antibiotics present different situations depending on the type of antibiotic, detection level, national regulations, etc., and there are still no harmonized regulations to deal properly with the possible hazards at the international level, even if specific regulations exist at the national level. Unapproved antibiotics (extra-label use of antibiotics) encompass two main situations that could be described as follows:

(i) Extra label use of an approved antibiotic in aquaculture (e.g. for a species, for a period or for doses for which it has not been specifically approved). There are countries that admit this type of extra-label use provided it is done under the responsibility of a certified professional (e.g. a veterinarian). However, there are also countries that do not accept this type of extra-label use of antibiotics.

(ii) Extra-label use of an antibiotic not specifically approved for use in aquaculture (e.g. an antibiotic approved for use in humans). Again, in some countries it could be accepted that a certified professional under his/her responsibility could decide on this type of extra-label use. In other countries (e.g. EU), this type of extra-label use is not allowed.

In both cases, the main problem is if the professional (or person) taking the decision to utilize an antibiotic in an extra-label form has or not the specific background information in order to produce a safe fish. In the first case (extra-label use of approved antibiotics), it has to be assured that residue levels in fish will be below the equivalent approved residue levels. In the second case (extra-label use of unapproved antibiotics), it has to be assured that the residue levels (wherever they occur) do not present a relevant risk to consumers.

Countries that do not accept the extra-label use of antibiotics assume that single professionals are usually not in a position to provide such assurances in all possible situations. Moreover, the possibility of the extra-label use of a given antibiotic in a given country does not mean generic approval for such an antibiotic. Each extra-label use shall always be under the responsibility of a certified professional and therefore from a formal point of view, the extra-label use of antibiotics, even if permitted, could be a violation if a proper certified professional is not involved.

Regardless of the discussion on extra-label use of antibiotics, it is necessary to underline that veterinarian prescriptions have proved to be a useful risk management tool for the responsible use of antibacterial drugs in aquaculture in Norway (Grave *et al.*, 1999).

Whereas the prescription scheme could be discussed and improved, most of the problems at the national and international level certainly come from the unregulated use of antibiotics. This could be due, for instance, to the use of non-approved or even banned antibiotics purchased "over-the-counter" (without the need for a prescription) or because of the undeclared use in fish feed formulations. The use of specifically banned antibiotics in aquaculture is a violation of regulations that, independently of any legal aspects that may exist, according to the specific regulation, can not be discussed in terms of compliance systems (i.e. it is a fraud). Hazards associated with the use of banned antibiotics enhance, in particular:

(i) Hazards due to the especially toxic nature of the antibiotic.

(ii) Hazards due to the development of resistance of a pathogenic microorganism of public health interest.

For instance, the ban on the use of chloramphenicol (CAP) for aquaculture purposes, which by now has been approved in most countries, is the typical case of an antibiotic that has revealed its toxic nature. CAP presents haematological toxicity in one of two ways – either as reversible bone marrow depression or an idiosyncratic aplastic anaemia. Of particular concern is aplastic anaemia, which is an idiosyncratic reaction that occurs in 1 out of every 25,000 to 40,000 courses of treatment. It is not related to dose or duration of therapy. Most cases have been associated with oral chloramphenicol, and the onset of aplasia may not occur until weeks or months after treatment with chloramphenicol has been discontinued (USP, 2000). As opposed to other substances, CAP has a quantitative indication of risk based on clinical medical records, and it is clear that it is not possible to define MRLs in such a case.

A number of antibiotics have been banned, either because they have been reserved for use in humans or because of their toxic effects. In the case of the USA, the following drugs are specifically banned for use in raising animals (FDA, 2002):

- (i) Chloramphenicol;
- (ii) Clenbuterol;
- (iii) Diethylstilbestrol (DES);
- (iv) Dimetridazole;
- (v) Ipronidazole;
- (vi) Other nitroimidazoles;
- (vii) Furazolidone, nitrofurazone, other nitrofurans;
- (viii) Sulphonamide drugs in lactating dairy cattle (except approved use of sulphadimethoxine, sulphabromomethazine, and sulphaethoxypyridazine);
- (ix) Fluoroquinolones; and
- (x) Glycopeptides.

The release of large quantities of antibiotics into the environment due to animal production (including aquaculture) and human use has produced the phenomena of microbial resistance, although different bacteria can acquire resistance to antibiotics and the development of antibiotic resistance by pathogenic bacteria is considered to be one of the most serious risks to human health at the global level (WHO, 2002).

The hazard in this case is clear, microbial illnesses that could be treated with a given antibiotic are no longer treatable with that antibiotic, when specific pathogenic bacteria have developed resistance. Many pathogenic bacteria already show multiple resistances, which means resistance to several antibiotics.

Attention in this case focuses on pathogenic bacteria that are clearly already relevant hazards according to epidemiological records. *Salmonella* spp. which are the most important pathogenic bacteria affecting humans through foods, including fish, is an obvious choice to consider. A recent study conducted by the US Food and Drug Agency (FDA) affiliates "indicates that antimicrobial-resistant *Salmonella* are present in imported foods, primarily of seafood origin (Zhao *et al.*, 2003), and stresses the need for continued surveillance of food-borne zoonotic bacterial pathogens from imported foods entering the United States". Fish analyzed in this study, and in which *Salmonella* resistant strains were found, encompassed 30 different fish species from both capture and aquaculture origins.

Whereas it is true that pathogen resistance to antibiotics is due to different sources (human and pet use, and animal production other than fish), and that caught fish can harbour resistant bacteria as well as aquacultured fish, a number of authors, as already mentioned, have already reported a correlation between findings of increased bacterial resistance levels on and around fish farms and the antimicrobial agents used at the farms.

Consequently, as is happening, for instance, with the use of antibiotics in human medicine, a full strategy to achieve responsible use of antibiotics in aquaculture seems necessary.

III – Hazards due to veterinary drugs other than antibacterials

There have been used and there are in use a number of (non-antibacterial) veterinary drugs in aquaculture. Possible hazards for humans come from residues in aquacultured fish, even though there are other possible hazards also mentioned in the literature, such as wild fish captured near aquaculture establishments having MRLs above those permitted by the regulations. The substances of concern are, in general, anti-parasitic agents, as well as anaesthetics, some chemicals and steroid hormones.

The regulatory situation of these substances around the world is also complex and not harmonized, with the presence of authorized substances, non-authorized substances, label and off-label uses (permitted or not), and specifically banned substances. The situation regarding these types of substances is perhaps more complex and unregulated than that of antibiotics.

Among the substances that appear as hazards for consumers are malachite green (MG), and its metabolite leucomalachite green (LMG). MG is a synthetic fabric dye that has been found effective for the treatment of parasitic and fungal infections in fish and shellfish and is used in aquaculture in many countries around the world. It is relatively inexpensive and in many countries is freely available.

A study performed recently by the National Toxicology Program of the United States (NTP, 2005) concluded that malachite green chloride might have caused tumours of the thyroid gland, liver and mammary gland in female rats (but did not cause cancer in female mice). LMG on the other hand might have caused cancers of the thyroid gland in male and female rats, of the testes in male rats and the liver in female rats (LMG also caused increased cancer in the liver of female mice). There are a number of other studies about the toxicity of MG and LMG (reviewed by Srivastava *et al.*, 2004), and there is little doubt about the carcinogenicity of both in laboratory animals.

MG and LMG are also suspected to be potential *in vivo* mutagens, which means with the possibility to damage genetic material, and they are therefore potentially carcinogenic to humans (Srivastava *et al.*, 2004), however, a study by the National Toxicology Program of the United States (NTP, 2004), concluded that MG was not mutagenic in any of several strains of *Salmonella typhimurium*.

In addition to the discussions about toxicological data, MG has never been a licensed veterinary medicine in many countries, which in turn makes it difficult to analyze for possible MRLs². To replace MG with authorized drugs would be the most advisable approach. The use of MG only in hatcheries raises the question that MG, and particularly LMG, could remain in sediments and be released when sediments are disturbed. Although the general tendency is towards the ban of MG and LMG, the legal status of MG is not uniform around the world. In some countries it is authorized for the treatment of fungal infections on fish eggs, but not on adult fish, whereas in other countries it is not authorized.

Other substances that may pose a hazard are, for instance, formaldehyde (FA), copper sulphate, potassium permanganate and hydrogen peroxide. Copper sulphate and potassium permanganate do not usually represent a high regulatory priority (the estimated risk is very low in current situations), whereas hydrogen peroxide is, in general, considered a low priority.

FA is an authorized veterinary drug in a number of countries that presents a special case. It is known that FA in some situations is a toxic (carcinogenic) substance that could be produced naturally in small quantities in fish muscle, and it is also part of the fish smoking process. Therefore, there is the possibility that cultured fish and, in particular, smoked aquacultured fish could present unusually high FA values by accumulation from different sources. Some countries (Australia and New Zealand) have an FA residue limit for smoked fish, whereas other countries (notably some Latin American countries) ask for absence of FA. Although proper risk assessments of FA residues in aquaculture fish do not exist, it also constitutes an example of a chemical hazard that could be enhanced along the production-processing line.

For other veterinary (or human) drugs that could be present as residues it should be mentioned that most regulations (e.g. EU) ban them as residues in fish. In particular, substances having anabolic effects on humans, as well as other medicines (for instance, stilbenes and their derivatives, antithyroid agents, steroids, beta-agonists, resorcylic acid lactones), are banned. The presence of these types of substances in aquacultured fish, in addition to the possible use of some of them as veterinary fish drugs, could also be due to an environmental hazard

² In addition to the technical and economic difficulties related to registering a non-approved veterinary drug *in use* (including the determination of an accepted MRL), there could also be legal aspects involved. Furthermore, in some legal contexts, there is no sense in banning a substance that has not been previously approved, because a non-approved substance cannot be used anyway. The ban of MG in some countries implied just such a type of situation.

associated with the quality of water utilized by fish culture. Large urban settlements near by, floods, or eventual inland water flows or coastal currents may lead to the possibility of this type of hazard.

IV – Conclusions

This paper has briefly reviewed the hazards that could be associated with the residues of veterinary drugs, either in aquacultured fish or as the result of aquaculture activities in the environment. Since there is no harmonized regulatory view around the world, it is difficult to extract "universal" approaches. However, consumers and regulatory bodies are becoming more and more aware of the different hazards, regardless of whether they could be listed as regulatory hazards or not.

The HACCP approach, and in general HACCP-based regulations (or, in general, food laws and regulations based on risk analysis) will make it unavoidable for aquaculture producers to develop their own hazard analysis regarding the use of specific veterinary drugs, whereas specific risk assessments will look into specific risk-product pair combinations. This view is very important, particularly with the continuous shift of responsibility from regulatory bodies to producers, especially since the introduction of HACCP-based regulations is expected to continue in the future. *A responsible utilization of approved drugs is therefore the best approach the aquaculture industry could adopt.*

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