SPECIAL GUEST EDITOR SECTION

A Review of Aquaculture Practices and Their Impacts on Chemical Food Safety from a Regulatory Perspective

Joe O. Boison
Canadian Food Inspection Agency (CFIA), Centre for Veterinary Drug Residues (CVDR) Laboratory, 116 Veterinary Rd, Saskatoon SK, S7N 2R3
Sherri B. Turnipseed
U.S. Food and Drug Administration, Office of Regulatory Affairs, Animal Drugs Research Center, Denver Federal Center Bldg 20, W. 6th Ave and Kipling St, Denver, CO 80225

Aquaculture is currently one of the most rapidly growing food production industries in the world. The increasing global importance for this industry stems primarily from the fact that it is reducing the gap between the supply and demand for fish products. Commercial aquaculture contributes significantly to the economies of many countries since high-value fish species are a major source of foreign exchange. This review looks at the aquaculture industry, the issues raised by the production of fish through aquaculture for food security, the sustainability of the practice to agriculture, what the future holds for the industry in the next 10–20 years, and why there is a need to have available analytical procedures to regulate the safe use of chemicals and veterinary drugs in aquaculture.

Farmed food fish for human consumption include finfishes, molluscs, crustaceans, amphibians (frogs), aquatic reptiles (except crocodiles), and other aquatic animals such as sea urchins, sea squirts, and jellyfishes. They also include but are not limited to fry (newly hatched) for recreational fishing and natural fisheries, ornamental fish and plants for the aquarium trade, raw materials for energy and biochemicals (algal extracts and pigments), and a number of items for the fashion and cosmetic industry (shell buttons and pearls). The Food and Agriculture Organization (FAO) definition of aquaculture is the "farming of aquatic organisms including fish, molluscs, crustaceans, and aquatic plants" (1). Farming implies some sort of intervention in the rearing process to enhance production, such as regular stocking, feeding, and protection from predators. It also implies individual, public, government, or corporate ownership of the stock being cultivated. For statistical purposes, aquatic organisms that are harvested by an individual or corporate body that has owned them throughout their rearing period contribute to aquaculture while aquatic organisms that are exploitable by the public as a common property resource, without appropriate licences, are the harvest of fisheries. This review will examine only aquaculture and not capture fisheries. In a recent report to the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), the 78th JECFA [The Joint World Health Organization (WHO)/FAO Expert Committee on Food Additives] advised that the term "fish" should be used when a maximum residue limit (MRL) recommendation applies to multiple species of finfish, while the term "mollusc" should be applied when other seafood is implied such as clams, oysters, and scallops. The term "crustacean" should be used when MRLs are recommended for species such as shrimp, prawn, and crayfish. The CCRVDF also considered that it may also be appropriate to identify some representative species of fish such as salmon, and of seafood such as shrimp (crustacean), as "major species" of fish and seafood, respectively (2).

During the last three decades, world aquaculture production increased from 5 to 63 million tonnes. Globally, fish represents about 16.6% of animal protein supply and 6.5% of all protein for human consumption (3). Usually fish is low in saturated fats, carbohydrates, and cholesterol and provides not only high-value protein but also a wide range of essential micronutrients, including vitamins D, A, and B; minerals (calcium, iron, iodine, zinc, and selenium); and polyunsaturated omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid). Thus, even when it is consumed in small quantities, fish can be effective in providing essential amino acids, fats, and micronutrients that are scarce in vegetable-based diets and among the poor and vulnerable populations around the globe. There is evidence of beneficial effects from fish consumption with respect to coronary heart disease (4), stroke, age-related macular degeneration, mental health (5, 6), growth, and development particularly for women and children during gestation and infancy for optimal brain development of children (7). Aquaculture has helped to produce more food fish, kept the overall price of fish down, and made fish more accessible to consumers around the world. But supplying fish sustainably without depleting productive natural resources and damaging the precious aquatic environment is a huge challenge.

Diseases Associated with Aquaculture

Aquaculture is susceptible to adverse impacts of disease, economic conditions, and natural disasters. Disease outbreaks in recent years have affected farmed Atlantic salmon in Chile, oysters in Europe, and marine shrimp farming in several countries in Asia, South America, and Africa, resulting in partial or sometimes total loss of production. Tropical storms, droughts, and floods have caused severe damage or production losses to the aquaculture industry in countries prone to natural disasters.

Guest edited as a special report on "Methods of Analysis for Residues and Chemical Contaminants in Aquaculture" by Joe Boison and Sherri Turnipseed.
Corresponding author's e-mail: joe.boison@inspection.gc.ca
DOI: 10.5740/jaoacint.15-033

In 2010, China's aquaculture industry suffered production losses of 1.7 million tonnes caused by natural disasters, diseases, and pollution. Disease outbreaks virtually wiped out the marine shrimp farming production in Mozambique in 2011 (3).

Veterinary Drugs in Aquaculture

Infectious disease is an ever-present hazard in aquaculture, with the potential to cause both major stock losses and problems of animal welfare. The most effective approach to control infectious diseases in aquaculture is to prevent the introduction of disease-causing pathogens. Good aquaculture management practices are essential to maintain a healthy aquaculture. When disease occurs, veterinary medicines are used to control the impact. For intensive aquaculture, vaccines are increasingly used in preference to chemotherapeutants. But where chemotherapeutants are used, in most areas their use is strictly controlled under the same regulatory code as other veterinary medicines. As a relatively new area, intensive aquaculture did not initially justify the development of chemotherapeutants specifically for use in aquaculture. Rather, pharmaceutical companies have tended to offer products developed for other areas of veterinary medicine for use in aquaculture. The potential hazards associated with the presence of antimicrobial drug residues in edible tissues from aquaculture products include changes in colonization patterns of human-gut flora, acquisition of drug resistance in pathogens in the human body, allergies, and toxic effects. Like other veterinary medicines, wherever there is an effective regulatory regime, authorization for the use of antimicrobials in aquaculture follows established processes. These include specifying the species, diagnosis, dose, duration, and withdrawal period to be observed when an antibiotic is used as a therapeutic agent. The establishment of appropriate withdrawal periods ensures that no harmful residues remain in edible tissues after use of a chemotherapeutant. Table 1 lists some of the veterinary drugs permitted to be used for aquaculture in the United States and Canada. For example, florfenicol, marketed under the trade name Aquaflor, is approved in Canada and the United States for the treatment of furuncolosis caused by susceptible strains of *Aeromonas salmonicida* in salmon with a specified withdrawal period of 12 days for fish maintained at water temperatures >5°C. Oxytetracycline is permitted for the treatment of ulcer caused by *Haemophilus piscium,* furuncolosis caused by *A. salmonicida*, and columnaris disease caused by *Chodrococcus columnaris.* It is also permitted to be used to treat cold-water disease caused by *Cytophaga psychrophila* and enteric redmouth disease caused by *Yersinia ruckeri* in salmon and trout. Treated fish must not be released or slaughtered for food for at least 40 days (when the water temperature is ≥10°C) or 80 days (for temperatures <10°C) after the last treatment. The same product may be used as an aid to prevent and treat gaffkemia caused by *Aerococcus viridans* in lobsters held in cars or pounds. Treated lobsters must not be marketed for use in food for at least 30 days after the last treatment. Sulfadimethoxine formulated together with the sulfa drug potentiator ormetoprim is marketed in Canada for the treatment of furunculosis in salmonids caused by *A. salmonicida.* Treated fish must not be released as stocker fish or slaughtered for use in food for at least 42 days after the last treatment when the water temperature is ≥10°C. It is not to be used if the water temperature is <10°C. A similar product manufactured by a Norwegian Company for use in medicated feed for control of enteric septicemia of catfish caused by *Edwarsiella ictaluri* and furunculosis in salmonids caused by *A. salmonicida* has a 42 day withdrawal period for salmonids and 3 days for catfish. Emamectin benzoate is registered for use as a veterinary drug in the treatment of sea lice infestations in Salmonidae and other finfish in several countries. It is used as a premix coated onto nonmedicated fish feed pellets to achieve an intended dose of 50 μg/kg of fish biomass/day for 7 days. It can be used for up to 3 times/year with a maximum of five treatments in any 2-year growth cycle. In Canada, it is marketed as SLICE® for use as an aid in the treatment of parasitic infections caused by all parasitic stages (chalimus I–IV and adult) of the sea louse on Atlantic salmon. No preslaughter withdrawal is required when used according to label directions.

MRLs for Compounds Approved for Aquaculture Use

Even with the few veterinary drugs approved for use in aquaculture, it is important for users of these drugs for fish production to respect and obey the withdrawal period guidelines to prevent residues of the approved drugs from entering the food chain. In addition to specifying withdrawal periods for approved usage, an MRL has been established that provides a concentration of the veterinary drug residue in a food matrix that is considered to be safe for the consumer. The establishment of MRLs at the international level is the responsibility of the CCRVDF; at the domestic level, it is the responsibility of the national government. The MRL is based on the type and amount of residue considered to be free from any toxicological hazard for human health, as expressed by the acceptable daily intake (ADI) or by a temporary ADI that utilizes an additional safety factor. Also, the MRL may be reduced so as to be consistent with good practice in the use of veterinary drugs, and to the extent that practical analytical methods are available. Establishing MRLs for fish presents several problems, including the identification of what are edible tissues and the complex pharmacokinetic properties and metabolism of veterinary drugs in fish. Table 2 lists some of the MRLs that have been established by the Codex Alimentarius Commission (CAC) and national authorities to protect consumers and facilitate global trade in aquaculture and aquaculture products. It identifies the species for which the active drug is permitted to be used, the marker residue to be monitored for regulatory compliance, and the tissue matrix for which the MRL has been set. For example, the CAC has established MRLs for aquaculture species for the administration of oxytetracycline to fish and giant prawn, deltamethrin in salmon, and emamectin benzoate in salmon and trout. MRLs of approved antibiotics are usually conservative. Processing, cooking, and frozen storage can reduce the residual levels of antibiotics. However, data regarding the effect of processing, cooking, and freezing of aquatic animal products on the degradation of antibiotic residues in aquatic animal products are scarce; it is therefore essential to conduct proper exposure assessments, in the form of risk assessments, not only to understand the risks but also to reassure consumers. The data required to enable the determination of an appropriate MRL are costly to produce. As different animals may take up, deplete, and metabolize antimicrobials differently, MRLs are generally specific to species and tissue type. However, because aquaculture does not generally generate sufficient sales income

Table 1. Approved aquaculture veterinary medicinal products with label instructions including indications of use and withdrawal periods

Drug name	Active veterinary ingredient(s)	Country	Species	Indications	Withdrawal period
Aquaflor CAI (Intervet, Inc./Schering-Plough Animal Health)	Florfenicol	U.S.	Catfish from fingerling to food fish, as the sole ration for 10 consecutive days	For use in medicated feed for the control of mortality in catfish due to columnaris disease associated with *Flavobacterium columnare*	Twelve days minimum withdrawal
Aquaflor	Florfenicol	Canada	Salmon	Treatment of furuncolosis caused by susceptible strains of *Aeromonas salmonicida* in salmon	Treated fish must not be harvested for use in food, or released as stocker fish for at least 12 days after the latest treatment. Not to be used in fish maintained at water temperatures <5°C
Oxysol-220 or Oxysol-440	Oxytertracycline HCl	Canada	Lobsters	Aid to prevent and treat gaffkemia caused by *Aerococcus viridans* in lobsters held in cars or pounds	Treated lobsters must not be marketed for use in food for at least 30 days after the latest treatment
OxyMarine -343 (Alpharma, Inc.) Oxytetracycline HCl soluble Powder-343 (Teva Animal Health) Teraramycin-343 (Aquatic Health Resources) TETROXY (Cross Vetpharm Group, N. Dublin, Ireland)	Oxytetracycline HCl	U.S. and Northern Ireland	Finfish fry and fingerlings lobsters	Administered by immersion for use to mark skeletal tissue as an aid in identification	
Terramycin-Aqua	Oxytetracycline HCl	Canada	Salmonids (salmon and trout)	Treatment of ulcer caused by *H. piscium,* furuncolosis caused by *A. salmonicida* columnaris disease caused by *Chodrococcus columnaris,* cold water disease caused by *Cytophaga psychrophila,* and enteric redmouth disease caused by *Yersinia ruckeri* in salmon and trout.	Treated fish must not be liberated or slaughtered for food for at least 40 days (when the water temperature is ≥10°C) or 80 days (for temperatures <10°C) after the last treatment
Terramycin-Aqua	Oxytetracycline HCl	Canada	Lobsters	Aid to prevent and treat gaffkemia caused by *A. viridans* in lobsters held in cars or pounds	Treated lobsters must not be marketed for use in food for at least 30 days after the last treatment
SLICE	Emamectin benzoate	Canada	Atlantic salmon	As an aid in the treatment of parasitic infections ccaused by all parasitic stages (chalimus I-IV and adult) of the sea louse on Atlantic salmon	No preslaughter withdrawal required when used according to label directions. Atlantic salmon must not be treated more than once in the 60 days prior to first being harvested for food.
Romet-30	Sulfadimethoxine and ormetoprim	Canada	Salmonids	Treatment of furunculosis in salmonids caused by *A. salmonicida*	Treated fish must not be released as stocker fish or slaughtered for use in food for at least 42 days after the last treatment when the water temperature is ≥10°C. Not to be used if the water temperature is <10°C.
Romet-30 (Pharmaq AS)	Sulfadimethoxine and ormetoprim	Norway	Salmonids	Use in medicated feed for control of enteric septicemia of catfish caused by *E. ictaluri* and furunculosis in salmonids caused by *A. salmonicida*	Withdrawal days are 42 days for salmonids and 3 days for catfish
Sulfamerazine (Alpharma)	Sulfamerazine	U.S.	Trout (rainbow, brook, and brown)	To control furunculosis in trout	21 days before harvesting for marketing or stocking in stream open to fishing.
Tribrissen 40% powder	Trimethoprim and sulfadiazine	Canada	Salmon	Treatment of salmon disease caused by *Vibrio anguillarum*	Treated fish must not be released as stocker fish or slaughtered for use in food for at least 80 days after the last treatment

to support the production of such data, only a few species specific MRLs have been established for fish.

Enforcement Programs for Regulatory Compliance

Compliance with MRLs for products from aquaculture is enforced by national authorities. For instance, the European Union (EU) has implemented a monitoring program in which fish muscle tissues are routinely sampled for the presence of a range of veterinary drug residues. With the trend towards increasing harmonization of international food safety standards for aquaculture products, regional monitoring programs have become more common. Such monitoring programs help provide assurance that no unacceptable human health risk is posed by veterinary drug residues in aquaculture products. Unfortunately, some countries implement monitoring programs for export products only, but do not offer the same assurance for domestic markets. Some jurisdictions such as the European Community and countries like Canada and Norway have approved a limited number of antibiotics specifically for use in aquaculture. In Canada, the antibiotics approved for aquaculture use are oxytetracycline, sulfadiazine (+ trimethoprim), sulfadimethoxine (+ ormetoprim), teflubenzuron, emamectin benzoate, ivermectin, azamethiphos, and florfenicol (8–10). The British Columbia Ministry of Agriculture has a valuable website with information on aquaculture and, in particular, the use of antibiotics in aquaculture (11). Japan has posted a wide range of aquaculture MRLs for fish and shellfish that include oxytetracycline, spiramycin, ethoxyquin, quinoclamine, deltamethrin, and flumequine (12). India has published MRLs for tetracycline, oxytetracycline, trimethoprim, and oxolinic acid for use in aquaculture. In the United States (13), chorulon, florfenicol, tricaine methanesulfonate, oxytetracycline, sulfamerazine, and sulfadimethoxine (+ trimethoprim) are approved for use in aquaculture production. In the United Kingdom, four antimicrobials, namely, oxytetracycline, oxolinic acid, amoxicillin, and cotrimazine (trimethoprim + sulfadiazine) are licensed for use in fish. In Norway, a slightly larger range of antimicrobials (benzylpenicillin + dihydrostreptomycin, florfenicol, flumequine, oxolinic acid, oxytetracycline, and cotrimazine) is permitted.

Inorganic and Organic Chemicals and Disinfectants Used in Aquaculture

In addition to diseases, chemical hazards can be present in aquaculture products through exposure to compounds used in the aquaculture system itself to prepare the ponds, disinfect equipment to maintain hygiene, increase the concentration of oxygen, and treat diseases. These compounds are generally considered to be safe to the fish and used for healthy management of the ponds or water. They can also be present in aquaculture products by acute and chronic pollution of waterways or sources of water. In this review, only those chemicals that impact the safety of aquacultured fish and fish products intended for human consumption will be discussed. The impact of these chemicals on the occupational health issues associated with the individuals working with these products fall outside of the scope of this presentation.

Chemical Fertilizers and Disinfectants

Chemical fertilizers, which may be organic or inorganic in nature, are widely used in semi-intensively managed ponds in the tropics and subtropics to stimulate phytoplankton blooms (14). Fertilizers, which include urea, ammonium sulfate, sodium and potassium nitrate, calcium, and ammonium phosphate, sodium silicate, and trace elements zinc, iron, copper, boron, and molybdenum, are highly water soluble, and they increase the concentrations of nitrate, ammonia, phosphate, potassium and silicate. Although some of the active compounds in these fertilizers may themselves be considered as hazards, they pose no risk to food safety in aquaculture products when used according to Good Agricultural Practice (GAP). Agricultural limestone (i.e., pulverized calcium carbonate or dolomite), lime (i.e., calcium/magnesium oxide), and hydrated lime (calcium/magnesium hydroxide) are usually applied to coastal shrimp-pond waters and soils, and to a lesser extent inland aquaculture ponds, to regulate pH and to sterilize pond soils between production cycles. Other agrochemicals, such as potassium permanganate, hydrogen peroxide and calcium peroxide, calcium hypochlorite, and sodium nitrate, are used as oxidizing agents in ponds to control phytoplankton, kill disease organisms, or oxidize bottom soils (14, 15). Aluminum sulfate (alum), ferric chloride, calcium sulfate (gypsum), and zeolite are applied as flocculants/coagulants to pond waters to cause suspended clay particles to precipitate in order to clear the water of turbidity (14, 16), while sodium chloride and gypsum are applied as osmoregulators to water to increase the salinity or the calcium concentration and improve conditions for normal osmoregulation by certain aquaculture species even though their use is rare. When used according to GAP, none of the above water treatment compounds can be considered hazardous to the consumer of aquaculture products. Copper, usually in the form of copper sulfate, and triphenyltin are used in aquaculture as molluscicides during the preparation of ponds before flooding and stocking (17). Ponds are usually limed at the same time, and the resulting high pH prevents high concentrations of copper in the water. In addition, as vertebrate fish can regulate the metal content of their tissues, the treatment of ponds with copper does not pose a risk to consumers of such fish. Crustacean shellfish, however, concentrate copper in edible tissues, including the hepatopancreas, and metal contamination in crustaceans may, therefore, pose a small risk for food safety. Available data show that the copper content of farmed crustaceans is higher than that of farmed vertebrate fish from similar environments. However, it is not possible to quantify the risk to human health. Tributyltin has been used in marine aquaculture as an antifouling agent for nets and cages (18). However, after it was shown that salmon in treated pens could accumulate tin in their tissues, the use of tributyltin for this purpose was banned in Europe and North America. Disinfectants such as benzalkonium chloride, polyvidone iodine (polyvinylpyrrolidone–iodine complex), glutaraldehyde, formalin, and hypochlorite are widely used in aquaculture to disinfect both portable equipment and holding units, generally in the interval between stockings. Because these compounds are washed away or decompose before restocking

Table 2. MRLs established by some national authorities and expert bodies for aquaculture production

Compound	Country	MRL, µg/kg	Tissue	Species	Marker residue
Ampicillin	EU	50	Muscle and skin in natural proportions	Fin fish	Ampicillin
Benzylpenicillin	EU	50	Muscle and skin in natural proportions	Fin fish	Benzylpenicillin
Cloxacillin	EU	30	Muscle and skin in natural proportions	Fin fish	Cloxacillin
Colistin	EU	150	Muscle and skin in natural proportions	Fin fish	Colistin
Cypermethrin	EU	50	Muscle and skin in natural proportions	Salmonidae	Cypermethrin (sum of isomers)
Danofloxacin	EU	200	Muscle and skin in natural proportions	Fin fish	Danofloxacin
Deltamethrin	60th JECFA (2003)	30	Muscle	Salmon	Deltamethrin
	EU	10	Muscle and skin in natural proportions	Fin fish	Deltamethrin
	Japan	30	Muscle	Salmon	
Dicloxacillin	EU	300	Muscle and skin in natural proportions	Fin fish	Dicloxacillin
Difloxacin	EU	300	Muscle and skin in natural proportions	Fin fish	Difloxacin
Diflubenzuron	EU	1000	Muscle and skin in natural proportions	Salmonidae	Diflubenzuron
Emamectin	78th JECFA (2013)	100	Muscle (fillet with skin)	Salmon and trout	Emamectin B1a
	EU	100	Muscle and skin in natural proportions	Salmonidae	Emamectin B1a
	EU	100	Muscle and skin in natural proportions	Fin fish	
Enrofloxacin	EU	100	Muscle and skin in natural proportions	Fin fish	Sum of enro- and ciprofloxacin
Erythromycin	EU	200	Muscle and skin in natural proportions	Fin fish	Erythromycin A
Ethoxyquin	Japan	1000		Salmoniformes such as salmon and trout	Ethoxyquin
	Japan	1000		Anguilliformes such as eel	Ethoxyquin
	Japan	1000		Perciliformes such as bonito, mackerel, sea bass, sea brean, and tuna	Ethoxyquin
	Japan	200		Crustaceans	Ethoxyquin
Florfenicol	EU	1000	Muscle and skin in natural proportions	Fin fish	Sum of florfenicol and its metabolites measured as florfenicol-amine
Flumequine	66th JECFA (2006)	500	Muscle	Trout	Flumequine
	66th JECFA (2006)	500 (temporary)	Muscle	Black Tiger shrimp and shrimp	The MRLs are temporary for Black Tiger shrimp and shrimp. The MRLs for shrimp applies to all fresh-water and marine shrimp
	EU	600	Muscle and skin in natural proportion	Fin fish	Flumequine
	EU	150 µg/kg	Muscle and skin	Salmonidae	Flumequine Provisional
	Japan	500	Muscle	Trout	Flumequine
Lincomycin	EU	100	Muscle and skin in natural proportions	Fin fish	Lincomycin
Neomycin	EU	500	Muscle and skin in natural proportions	Fin fish	Neomycin
Oxacillin	EU	300	Muscle and skin in natural proportions	Fin fish	Oxacillin
Oxolinic acid	EU	100	Muscle and skin in natural proportions	Fin fish	Oxolinic acid
Oxytetracycline	58th JECFA (2002)	200	Muscle	Fish	Oxytetracycline
	58th JECFA (2002)	200	Muscle	Giant prawn	Oxytetracycline
	Japan	200	Muscle	Salmoniformes such as salmon and trout	Oxytetracycline
	Japan	200		Anguilliformes such as eel	Oxytetracycline

Table 2. (*continued*)

Compound	Country	MRL, µg/kg	Tissue	Species	Marker residue
	Japan	200		Perciliformes such as bonito, horse mackerel, mackerel, sea bass, sea bream, and tuna	Oxytetracycline
	Japan	200		Shelled molluscs	Oxytetracycline
	Japan	200	Muscle	Crustaceans	Oxytetracycline
	Japan	200		Other aquatic animals	Oxytetracycline
Paronomycin	EU	500	Muscle and skin in natural proportions	Fin fish	Paronomycin
Quinoclamine	Japan	200		Fish and shellfish	Quinoclamine
Sarafloxacin	EU	30	Muscle and skin in natural proportions	Salmonidae	Sarafloxacin
Spectinomycin	EU	300	Muscle and skin in natural proportions	Fin fish	Spectinomycin
Spiramycin	Japan	200			Spiramycin
Teflubenzuron	EU	500	Muscle and skin in natural proportions	Salmonidae	Teflubenzuron
Thiamphenicol	EU	50	Muscle and skin in natural proportions	Fin fish	Thiamphenicol

and do not come into contact with fish, they present no risk to consumers.

Chlorinated Hydrocarbons

When chronic contamination in aquaculture occurs through the use of polluted water supplies, leaching of agricultural or industrial chemicals from treated or contaminated soils into surface waters, and deposition from the atmosphere, the problem is generally very difficult to resolve. A wide range of chlorinated compounds can be present in the aquatic environment, but chlorinated insecticides [e.g., dieldrin, lindane, dichlorodiphenyltrichloroethane (DDT) and their degradation products], polychlorinated biphenyls (PCBs), and polychlorinated dibenzodioxins and polychlorinated dibenzofurans are three groups of compounds of particular concern to environmentalists and public health officials. Although there is a large volume of literature on the presence and fate of chlorinated organic compounds in the aquatic environment and biota, most data relate to the natural environment, and very little has been published on chlorinated compounds in aquaculture systems or aquaculture products. Pesticides like DDT and lindane have been extensively used in Asian countries for control of agricultural pests and the mosquito vectors of malaria. Although the use of such chlorinated insecticides has been or is being phased out in these countries, chlorinated hydrocarbons are very persistent in soils and will continue to leach out into surface waters for a considerable period. PCBs, polychlorinated dibenzodioxins, and polychlorinated dibenzofurans are of widespread occurrence. Now that the hazards of PCBs are known, their production has been banned. The dioxins and furans, however, are generated as products of combustion, such as the burning of wood in forest fires or as cooking or heating fuel or as by-products of the production of other chlorinated chemicals. They can, therefore, enter the aqueous environment as effluents or through deposition from the atmosphere. Data are available on the concentrations of these chemicals in fish from wild stocks, but a literature search revealed very scanty data on their concentrations in aquaculture products. Although dioxins and furans are mostly produced in developed countries and most aquaculture is conducted in less developed countries, these highly chlorinated hydrocarbons are globally distributed by atmospheric transport. Their physical properties are such that they are appreciably volatile from the water phase and therefore tend to accumulate in the Polar Regions. This property reduces the relative concentration of organochlorines in tropical waters, where most farmed fish are cultivated. With the exception of chlorinated hydrocarbons, most industrial chemicals and agrochemicals are readily degraded by chemical and biological processes in soils and waters, do not bioaccumulate to any large extent, and are rapidly eliminated from fish.

Challenges Facing the Aquaculture Industry

The critical challenges facing the global food and agricultural sector are summarized in the World Bank Group (WBG) Report on Prospects for Fisheries and Aquaculture: Fish to 2030 (19). In that report it is projected that the global population will reach 9 billion by 2030, and the world food-producing sector must secure food and nutrition for the growing population through increased food production and reduced waste. It was also recommended in that report that production increases will have to occur under conditions where resources necessary for food production, such as land and water, will be even scarcer in a more crowded world. Thus, the sector will need to be far more efficient in utilizing productive resources. Further, in the face of global climate change, the world, and therefore aquaculturists, will be required to change the ways they conduct economic activities. Aquaculture must address many of these difficult challenges.

One of the difficult challenges aquaculture faces is that fish is highly perishable. Therefore, it needs timely harvesting and procurement, advanced storage, processing and packaging facilities, and efficient transportation for its marketing. Particularly, specific preservation techniques and requirements must be adhered to in order to protect its nutritional quality, extend its shelf life, minimize spoilage by bacteria, and prevent losses caused by improper handling. Fish can also be processed into a wide variety of products to increase its economic value;

it is generally traded as live, frozen, fresh, chilled, heat-treated, dried, fermented, smoked, pickled, boiled, fried, freeze-dried, minced, powdered, or canned. The other challenge aquaculture faces is that it is extensively traded in international markets. According to the FAO, 38% of fish produced in the world was exported in 2010. In that year, 40.5% of the world fish production was marketed live, chilled, or fresh; 45.9% was processed in frozen, cured, or otherwise prepared forms for human consumption; and the remaining 13.6% was destined for nonhuman consumption. In 2010, the most important forms contributing 46.9% of the market share were live, fresh, or chilled fish followed by frozen fish at 29.3%, prepared or preserved fish at 14%, and cured fish at 9.8%.

Food Safety and Risk Analysis Associated with Aquaculture

Inherent in all human activities, including activities related to food fish production, are hazards that may adversely affect people's health. The identification of hazards and the determination of their relevance for health, as well as their control, is the function of risk analysis. Risk analysis has emerged as the basis for assessing, managing, and communicating about risks associated with foodborne hazards. The rules that govern international trade in food were agreed to during the Uruguay Round of Multilateral Trade Negotiations and apply to all members of the World Trade Organization (WTO). With regard to food safety, rules are set out in the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS agreement). According to the SPS agreement, WTO members have the right to take legitimate measures to protect the life and health of their populations from hazards in food, provided that the measures are not unjustifiably restrictive of trade. Such measures need to be based on risk analysis and take into consideration risk analysis techniques developed by relevant international organizations such as the FAO and the WHO of the United Nations and the CAC. This may be achieved by following instructions provided in various guidance documents such as the Code of Practice for Fish and Fishery Products (20) developed by the Codex Committee on Fish and Fishery Products (CCFFP) and the basic texts on food hygiene (21).

Veterinary Drugs Not Permitted to be Used in Aquaculture Production

Malachite green (MG) and its metabolite leucomalachite green (LMG), gentian violet (GV) and its metabolite leucogentian violet (LGV), and chloramphenicol (CAP) are among the substances used in aquaculture production that have been determined by international regulatory and standard setting bodies to pose health related hazards to consumers. These are examples of compounds for which no ADIs could be established to permit the establishment of an MRL. MG is a synthetic fabric dye that has been found effective for the treatment for parasitic and fungal infections in fish and shellfish and has been used in aquaculture in many countries around the world for many years. It is relatively inexpensive and is easily available in many countries, but it is toxic to fish. In catfish, salmon, and eel, it is readily metabolized to LMG. The safety to use MG in food production was evaluated in 2008 by the 70th JECFA at the request of the 17th CCRVDF. The 70th JECFA determined that both MG and its metabolite LMG caused DNA adduct formation and that LMG caused cancer in female mice by a genotoxic mechanism. MG is readily metabolized to LMG (22). The JECFA determined that MG is to be considered a health related hazard because it is carcinogenic and there is no adequate margin of exposure to ensure protection of public health based on the use of MG in market size fish.

GV is also marketed as Basic Violet 3, crystal violet, and methyl violet 10B. It is a triphenylmethane dye with antibacterial, antifungal, and anthelminthic properties. GV has been used for the treatment of fungal and parasitic infections in fish and topically for skin and eye infections in livestock. However, several countries have withdrawn approval or registration of this use. GV is used in industrial processes for wood, leather, silk, nylon, ribbon, and paper tapes, and also as a biological stain. Thus, contamination of the environment can occur, as about 10–15% of all dyes are lost directly to wastewater in the dyeing process. GV in water originating from contamination as a result of its industrial applications or from its illegal use in aquaculture is efficiently taken up from the water by fish. The safety of use of GV in food production destined for human consumption was evaluated in 2013 by the 78th JECFA at the request of the 21st Session of the CCRVDF (21). The Committee noted that GV is structurally related to MG, and since it is known that LMG is a more potent carcinogen than MG, it is therefore possible that LGV is similarly a more potent carcinogen than GV. Also, because GV and LGV are readily interconvertible in the body, it is likely that exposure to GV will also result in exposure to LGV. The 78th JECFA concluded that GV is genotoxic and carcinogenic and that it is inappropriate to set an ADI and therefore an MRL for GV.

The safety of CAP in food was evaluated by the 12th JECFA (23), 32nd JECFA (24), 42nd JECFA (25), and 62nd JECFA (26). All the Committees observed that CAP is a health related hazard because of carcinogenicity, with the evidence of a genotoxic mechanism and epidemiological studies in humans showing that it is not possible to establish any dose relationship or threshold dose for the induction of a potentially fatal aplastic anemia. Therefore, 62nd JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs. Because there was no concentration in food including fish below which an exposure may be expected to be deemed safe, the CAC has, based on the 62nd JECFA assessment, recommended that national authorities should prevent residues of MG, GV, and CAP in food by not permitting their use in food producing animals.

In addition to these three compounds, national authorities have individually promulgated legislation to prevent the use of compounds not considered to be safe for food animal production as follows. In India, nitrofurans (furaltadone, furazolidone, furfurylamide, nifuratel, nifuroxime, nifurprazine, nitrofurantoin, and nitrofurazone), CAP, neomycin, nalidixic acid, sulfamethoxazole, *Aristolochia spp.* and preparations thereof, chloroform, chlorpromazine, colchicine, dapsone, dimetridazole, metronidazole, ronidazole, ipronidazole, other nitroimidazoles, clenbuterol, diethylstilbestrol (DES), sulfonamide drugs (except approved sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine), fluoroquinolones, glycopeptides, and other pharmacologically active substances are prohibited in the culture of or in any hatchery for producing the juveniles or larvae or nauplii of or in any unit manufacturing feed for or in any unit preprocessing or processing shrimp, prawns, or any variety of fish intended for exports (27). In the United States, the Center for Veterinary Medicine has identified a number of drugs and families of drugs known to be used in fish without U.S. Food and Drug Administration approval (28) that are on the high enforcement priority list. These drugs, which include CAP, nitrofurans, fluoroquinolones and quinolones, MG, and steroid hormones should not be used in fish that are to be consumed, unless a sponsor obtains an approval or index for them. The United States has also prohibited CAP, clenbuterol, DES, dimetridazole, ipronidazole and other nitroimidazoles, furazolidone and nitrofurazone, fluoroquinolones, and glycopeptides (28). None of these drugs has been approved for use in fish, for extra label use in food producing animals.

There are nine substances included in Annex IV of Regulation 2377/90/EEC that may not be used in food producing species in the EU because no safe level of residue can be determined: CAP, chloroform, chlorpromazine, colchicine, dapsone, dimetridazole, metronidazole, nitrofurans (including furazolidone), and ronidazole. The presence of an Annex IV substance residue (including metabolites) is prima facie evidence of the use of a prohibited substance in a food animal species.

The Future and Sustainability of Aquaculture

On the whole, the future of aquaculture looks quite promising. The responsibility for food safety associated with aquaculture products is shared among governments, the fish production and processing industries, and consumers. For its part, the aquaculture industry has instituted farm management programs, where appropriate, based on the principles of the HACCP (Hazard Analysis of Critical Control Points) system. Standard setting bodies, such as the CAC, have advocated a harmonized approach for the introduction of the HACCP system in the food sector, and the CCFFP has revised the Codes of Practice for Fish and Fishery Products to include the principles of HACCP. HACCP permits a systematic approach to the identification and assessment of hazards and risks associated with the production, distribution, and use of aquatic foods and puts the responsibility for the aquaculture of safe food products on the aquaculture sector. Therefore, when the system is applied at the production level, specific hazards and corresponding control measures can be identified and those measures can then be integrated into the production process. This should ideally lead to reduced requirements for end-product testing in an integrated farm-to-table food safety continuum, resulting in a cost-effective use of resources, increase consumer confidence in aquaculture products, and expanded market opportunities. It is therefore anticipated that with the development and implementation of GAPs, Good Manufacturing Practices, Good Hygiene Practices, and HAACP, the industry will succeed in minimizing the impacts of biological and chemical hazards inherent in aquaculture production, sustain the growing production trends, develop more viable systems that will increase the safety and security of the fish-eating consumer, and facilitate international trade.

The Need for Validated Analytical Methods

Even though the measures taken above should ideally lead to reduced requirements for end-product (i.e., laboratory or field) testing in an integrated food safety continuum, national surveillance programs have indicated that residual veterinary drugs and chemicals are still being detected in harvested aquaculture products. Therefore, to ensure that aquaculture products continue to be safe for human consumption and maintain the significant contribution to both domestic and international trade, regulatory laboratories have developed and validated analytical methods that are used to support this regulatory oversight of establishing MRLs and withdrawal periods for approved drug use in aquaculture. Because fish is globally traded, the CAC also prescribes that countries engaged in international trade must establish analytical laboratories that use analytical methods validated according to international standards and that the use of those methods must be embedded in a quality system that complies with International Organization for Standardization (ISO)/International Electrotechnical Commission (IEC) 17025:2005: Standard or Principles of Good Laboratory Practice. It is therefore not pure coincidence that regulatory laboratories invest a lot of their time and resources into developing and validating methods that generate results that can not only withstand the test of scientific scrutiny upon challenge in courts of law but are also deemed to be fit-for-purpose. With this in mind, all the methods included in this Special Section have either been validated according to international guidelines designed for single laboratories before they were applied to the analysis of any regulatory samples and/or have been demonstrated through a multilaboratory collaborative study that the method is rugged and can be used under different laboratory conditions around the globe.

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