AQUACULTURE CHEMICALS

1. Introduction

Intensive or extensive culture of aquatic animals requires chemicals that control disease, enhance the growth of cultured species, reduce handling trauma to organisms, improve water quality, disinfect water, and control aquatic vegetation, predaceous insects, or other nuisance organisms. The Aquaculture chemical needs for various species have been described for rainbow trout, *Oncorhynchus mykiss* (1); Atlantic and Pacific salmon, *Salmo salar* and *Oncorhynchus* sp. (2); channel catfish, *Ictalurus punctatus* (3); striped bass, *Morone saxatilis* (4); milkfish, *Chanos chanos* (5); mollusks (6); penaeid *Penaeus* shrimp (7); and a variety of other freshwater and marine species (8).

Laws and regulations on the use of chemicals in aquaculture vary by country and serve to ensure safe and effective use and protection of humans and the environment. Regulations and therapeutants or other chemicals that are approved or allowed for use in the United States, Canada, Europe, Japan, Chile, and Australia are presented below.

2. Regulation of Aquaculture Chemicals in the United States

In the United States, the U.S. Food and Drug Administration (FDA) and the U.S. Environmental Protection Agency (EPA) regulate the application of chemicals to organisms or to their environments. FDA controls the use of drugs and anesthetics and EPA controls the application of chemicals and pesticides to the environment. In cases that involve treatments to control pathogens that are present in the water, the jurisdiction becomes unclear and has been changed over time. Each agency develops appropriate guidelines and policies to implement the laws for its field of responsibility (9,10).

Therapeutant approval requires information on human safety, efficacy against target organisms, toxicity to nontarget organisms, residues in food-producing animals, and effects on the environment. Drugs for food-producing animals require information on metabolites and residue dynamics to establish tolerance levels and withdrawal times. Withdrawal time is the period of time that must pass after the last treatment or exposure to a certain drug, chemical, or pesticide before an animal can be consumed. Residue studies may not be necessary if the actual holding time of an aquatic animal is significantly longer than the required withdrawal period for a major species; examples include the treatment of eggs, fry, or small fingerlings long before they are harvested or slaughtered for food as adults. Studies to generate the required data must be conducted according to good laboratory practices (GLP) requirements and each drug must be produced and formulated with good manufacturing practices (GMP). Requirements of GLP and GMP significantly increase the cost of developing new drugs (9,10).

Most pharmaceutical and chemical companies do not try to gain approvals of aquaculture drugs because of increased costs for approval requirements,

limited sales and profit potential, diversity of cultured aquatic animals and diseases, and lack of uniform testing guidelines and data requirements among countries (9). To be profitable, an aquaculture drug must be marketed worldwide, but few nations accept data on aquaculture drugs that were tested in a foreign country and the required tests are too expensive to repeat in every country. Data on mammalian safety, environmental fate, residues, and metabolism are the most expensive to obtain and are not available for most of the drugs known to be effective on aquatic organisms. In fact about $3 million of the estimated $3.5 million spent to register a new drug in the United States is for these types of studies. There is a great need for international harmonization and cooperation to get drugs and chemicals registered for aquatic species (9,11). To that end, two international harmonization workshops were held in 1997 and 1998 and several special sessions on cooperative efforts at international aquaculture conferences have been organized (9).

3. Registered Aquaculture Chemicals in the United States

3.1. Antibacterials. Few therapeutants are registered in the United States for use on any cultured aquatic species (Table 1). In the most critical area of antibacterials, only two (Terramycin for Fish and Romet-30) are approved and available. Only the aquatic species and diseases listed on the label may be treated unless a veterinarian prescribes extra-label use for other aquatic species and their diseases. Terramycin (oxytetracycline) is legal to use against *Aeromonas*, *Hemophilus*, and *Pseudomonas* in salmonids and catfishes and gaffkemia in lobster (10,12). Romet-30 (sulfadimethoxine, ormetoprim) is labeled for the control of furunculosis in salmon and enteric septicemia in catfishes (10,12). Data are available for the control of enteric redmouth disease with Romet but have not been submitted to FDA for label inclusion. A range of bacteria has developed resistance to both compounds, and broad-spectrum antibacterial agents are needed as replacements.

3.2. Fungicides. Formalin is the only fungicide approved by FDA for use on eggs of all fish at 1,000–2,000 mg/L for 15 min (12). Delivery apparatus has been developed to reduce human exposure toformalin. Fish culturists in the Pacific Northwest have successfully used formalin to control fungal infections on salmon broodstock, but controlled research that indicates formalin is a good fungicide on adult fish of many species is lacking.

When it approved the New Animal Drug Application (NADA) of formalin, FDA ruled that use of formalin for fisheries was safe for humans and the environment. They ruled that effluents from fish treatments at 250 mg/L should be diluted 10 times and from egg treatments 100 times if 1,000–2,000 mg/L were used (12). Before approving the drug, FDA also addressed carcinogenicity by stating it was not concerned about human exposure from either water or fish treated with formalin. The U.S. Fish and Wildlife Service (USFWS) has procedural guidelines that should protect workers from harmful levels of formalin. Calculations based on treatment levels demonstrated that a fishery worker is exposed to not more than 0.117 mg/L formalin in the air, well below the levels

Table 1. **Chemicals Registered[a] or Allowed[b] for Use in Aquaculture in the United States by the FDA or the EPA[c]**

Product (trade or alternative name)	CAS Registry Number	Molecular formula	Use pattern	Tolerance[d]	Withdrawal time[e]	Comments
			Therapeutants			
acetic acid, glacial (vinegar)	[64-19-7]	$C_2H_4O_2$	parasiticide for fish. — 1000–2000 mg/L for 1–10 min	none established	none established	low regulatory priority
calcium chloride	[10043-52-4]	$CaCl_2$	osmoregulatory enhances for fish. — up to 150 mg/L	none established	none established	low regulatory priority
calcium oxide	[1305-78-8]	CaO	protozoacide—2000 mg/L for 5 s	none established	none established	low regulatory priority
formalin (Paracide-F, Parasite-S, Formalin-F)	[50-00-0]	CH_2O	parasiticide for all fish—25 mg/L in ponds; up to 250 mg/L for 1 h in tanks and raceways; fungicide for all fish eggs—1000–2000 mg/L for 15 min in egg-treatment tanks; protozoacide for penaeid shrimp—50–100 mg/L for up to 4 h in tanks and raceways; 25 mg/L in ponds	none required	none required	
hydrogen peroxide	[7722-84-1]	H_2O_2	fungicide for all fish and their eggs—250–500 mg/L	none required	none required	low regulatory priority
magnesium sulfate (Epsom salts)	[7487-88-9]	MgO_4S	monogenetic trematodes and external crustacean parasites—30,000 mg/L for 5–10 min	none established	none established	low regulatory priority
oxytetracycline (Terramycin for fish)	[79-57-2]	$C_{22}H_{24}N_2O_9$	antibacterial for salmonides and catfish and lobster—2.75–4.125 g/50 kg[f] per day for 10 d in feed	2 ppm in salmonids, catfish, and lobsters	21 d	
papain	[9001-73-4]		remove gelatinous matrix of fish eggs.— 0.2% solution	none established	none established	low regulatory priority
potassium chloride	[7447-40-7]	KCl	osmo regulatory enhancer for fish—10–2,000 mg/L	none established	none established	low regulatory priority

Table 1 (*Continued*)

Product (trade or alternative name)	CAS Registry Number	Molecular formula	Use pattern	Tolerance[d]	Withdrawal time[e]	Comments
sodium chloride (salt)	[7647-14-5]	NaCl	osmoregulatory enhancer for fish—0.5–1% for indefinite period; 3% for parasiticide. — 10–30 min	none established		low regulatory priority
sulfadimethoxine and ormetoprim (Romet-30, Romet-B)	[122-11-2]	$C_{12}H_{14}N_4O_4S$	antibacterial for salmonids and catfish—50 mg/kg per day for 5 d	0.1 ppm in salmonids and catfish	6 wks for salmonids, 3 d for catfish	has potential for use in other aquatic species
	[6981-18-6]	$C_{14}H_{18}N_4O_2$				
sulfamerazine (Sulfamerazine in Fish Grade)	[127-79-7]	$C_{11}H_{12}N_4O_2S$	antibacterial for salmonids —11 g/50 kg[g] per day for 14 d in feed; discontinued after 14 d	zero in edible tissues of trout	3 wks	no longer available
thiamine hydrochloride	[67-03-8]	$C_{12}H_{18}Cl_2N_4OS$	prevent thiamine deficiency in salmonids —up to 100 mg/L; for up to 1000 mg/L for up to 1 h	none established	none established	low regulatory priority
Disinfecting agents						
calcium hypochlorite (Olin HTH Dry Chlorinator Granular)	[7778-54-3]	$Ca(ClO)_2$	disinfectant and sanitizer in fish tanks, raceways, and on utensils—200 mg/L for 1 h; control of algae and bacteria in ponds— 5–10 mg/L residual chlorine for 12–24 h	none established		
didecyldimethylammonium chloride (Sanaqua)	[7173-51-5]	$C_{22}H_{48}ClN$	disinfection of aquarium and fish-holding equipment— 59 mL in 15 L[h] water for 10 min; disinfection in fish disease control institutions— 104 mL in 15 L for 10 min	none established	none established	do not use directly on fish or other aquatic life

povidone-iodine compounds	[25655-41-8]		disinfection of fish eggs— 50 mg/L for 30 min during water hardening 100 mg/L for 10 min after water hardening	none established		low regulatory priority
quaternary ammonum compounds		$C_{27}H_{42}ClNO_2$	disinfection of water, gear, and tanks—2 mg/L for 1 h	none established		not for use directly on fish or other aquatic life
(benzalkonium chloride)	[68424-85-1]					
(benzethonium chloride)	[121-54-0]					
			Water treatment compounds and dyes			
calcium chloride	[10043-52-4]	$CaCl_2$	increase water calcium concentration to ensure proper egg hardening— to increase 10–20 mg/L calcium carbonate	none established	none established	low regulatory priority
fluorescein sodium	[518-47-8]	$C_{20}H_{12}O_5$	dye to check water flows or dilution—0.1 mg/L	none established		exempted from registration by EPA
lime, slaked lime (calcium hydroxide)	[1305-62-0]	$Ca(OH)_2$	pond sterilant— 0.33 L/m2 (1.338 L/acre) of quick lime; 0.2 kg/m2 (1.784 lb/acre) of slaked lime	none established	none established	generally recognized as safe
(calcium oxide)	[1305-78-8]	CaO				
(calcium carbonate)	[471-34-1]	$CaCO_3$				
oxytetracycline (Terramycin)	[79-57-2]	$C_{22}H_{24}N_2O_9$	dye to mark fish	2 ppm in salmonids and catfish	7 d for oral, 15 d for injectable compounds	FDA ruled that there is no public health concern when used as directed
potassium permanganate	[7722-64-7]	$KMnO_4$	oxidizer and detoxifier— 2 mg/L	none established		exempted from registration by EPA
rhodamine B and WT	[81-88-9]	$C_{28}H_{31}ClN_2O_3$	dye to check water flows or dilution—20 μg/L	none established		exempted from registration by EPA

Table 1 (*Continued*)

Product (trade or alternative name)	CAS Registry Number	Molecular formula	Use pattern	Tolerance[d]	Withdrawal time[e]	Comments
sodium methanesulfonate (Amquel)	[2386-57-4]	$CH_4O_3S{\cdot}Na$	detoxifier of chlorine, ammonia, and chloramines	none established		FDA ruled that the compound is not a drug and therefore is not under FDA jurisdiction
			Spawning aids			
human chorionic gonadotropin (Chorulon)			spawning aid by intramuscular injection—50–510 IU/lb body wt for males 67–1816 IU/lb body wt for females	none required		veterinanian prescription only
			Anesthetics			
carbon dioxide gas	[124-38-9]	CO_2	anesthetic on fish— 200–400 mg/L for 4 min	none established		low regulatory priority
sodium bicarbonate (baking soda)	[144-55-8]	$NaHCO_3$	anesthetic for fish— 142–642 mg/L for 5 min	none established		low regulatory priority
tricaine methane sulfonate (Finquel; MS-222)	[886-86-2]	$C_{10}H_{15}NO_5S$	anesthetic for fish and amphibians—15–66 mg/L for 6–48 h for sedations; 50–330 mg/L for 1–40 min for anesthesia	none established	21 d	food fish use
			Herbicides and algicides			
acid blue and acid yellow (Aquashade)			algicide and herbicide	none established		also used to control off-flavors in fish
copper, elemental (Aquatrine, etc)	[7440-50-8]	Cu	algicide and antibacterial	none established	fish and shrimp may be harvested immediately	do not use in water containing trout; used as antibacterial on penaeid shrimp

copper sulfate (Calco Copper Sulfate, etc)	[7758-98-7]	$CuSO_4$	algicide and herbicide	none established		low alkalinity could cause the chemical to be hazardous to fish
2,4-D (Aquacide, Aqua-Kleen, etc)	[94-75-7]	$C_8H_6Cl_2O_3$	herbicide	1 ppm in fish and shellfish		
dichlobenil (Acme Norosac G-10, Casoron-10G)	[1194-65-6]	$C_7H_3Cl_2N$	herbicide	none established		nonfood fish use
diquat dibromide (Aqua-Clear, etc)	[2764-72-9]	$C_{12}H_{12}Br_2N_2$	algicide and herbicide	0.1 ppm in fish and shellfish		EPA proposed a maximum contaminant level (MCL) of 0.02 ppm for drinking water
endothall (Aquathol Granular, Aquathol K, etc)	[45-73-2]	$C_8H_{10}O_5$	herbicide	0.2 ppm in potable water	3 d	EPA proposed a MCL of 0.1 ppm for drinking water
fluridone (Sonar)	[59156-60-4]	$C_{19}H_{14}F_3NO$	herbicide	0.5 ppm in fish and crayfish		not for use in tidewater or brackish water
glyphosate (Rodeo)	[1071-83-6]	$C_3H_8NO_5P$	herbicide	0.25 ppm in fish		EPA proposed a MCL of 0.1 ppm for drinking water
			Piscicides			
antimycin (Fintrol Concentrate)	[27220-56-0]	$C_{26}H_{36}N_2O_9$	piscicide	none established		general fish toxicant; can also be used to selectively remove scaled fish from catfish ponds
rotenone (Chem-Fish Synergized, Prentox, etc)	[83-79-4]	$C_{23}H_{22}O_6$	piscicide	none established		general fish toxicant

Table 1 (*Continued*)

Product (trade or alternative name)	CAS Registry Number	Molecular formula	Use pattern	Tolerance[d]	Withdrawal time[e]	Comments
niclosamide (Bayluscide)	[1420-04-8]	$C_{13}H_8Cl_2N_2O_4$	piscicide; molluscicide	none established		piscicide only for use on sea lamprey in the Great Lakes area; molluscicide to control snails (vectors of swimmers itch, etc)

[a]A registered compound is an available commercial product bearing an EPA or FDA label specifying its allowed uses. Refs. 10 and 12.
[b]An allowed product does not necessarily have an EPA or FDA label because some other classification or designation may allow its use in aquatic situations (eg, Low Regulatory Priority drugs).
[c]Ref. 10, 12.
[d]Tolerance refers to residue levels of a drug or chemical that are permitted by regulatory agencies in food eaten by humans.
[e]Withdrawal time is the period of time that must pass after the last treatment or exposure to a certain drug, chemical, or pesticide before an animal can be consumed. None has been established if there is no notation.
[f]2.75–4.125 g/50kg= 2.5–3.75 g/100lb.
[g]11g/50 kg=10 g/100lb.
[h]59mL in15 L≈2 fl oz in 4 gal.

established by the U.S. Occupational Safety and Health Administration to protect workers.

Salt applied as equal parts of unionized sodium chloride and calcium chloride at 20 g total per L for 1 h, three times a week, has also been used to control fungal infections on eggs. The salt combination is first applied one day after fertilization to the first pick of eggs. The Center for Veterinary Medicine (CVM) categorized these compounds as unapproved drugs of Low Regulatory Priority (10). CVM is unlikely to object to the use of these drugs if the following conditions are met: (1) the drugs are used for the prescribed indications, including species and life stage where specified, (2) the drugs are used at the prescribed dosages, (3) the drugs are used according to good management practices, (4) the product is of an appropriate grade for use in food animals, and (5) an adverse effect on the environment is unlikely.

3.3. Parasiticides. Formalin is the only parasiticide currently approved for use on all fish and penaeid shrimp (12). It is registered for use on all fish at concentrations up to 250 mg/L for 1 h in tanks and raceways and 15 to 25 mg/L for an indefinite period in ponds and for penaeid shrimp at 50–100 mg/L for up to 4 h in tanks and raceways and 25 mg/L in ponds (12). A second chemical, trichlorfon (Masoten) was registered for use on nonfood fishes by EPA but is not currently available. Vinegar (glacial acetic acid) and salt (sodium chloride) are also used to control external parasites on fishes and CVM classifies these compounds as unapproved drugs of Low Regulatory Priority (10).

3.4. Disinfectants. Several disinfecting agents can be used in hatcheries and two are of particular interest. Because they are considered as unapproved drugs of Low Regulatory Priority by FDA, povidone-iodine compounds can be used to disinfect the surface of eggs (10). Benzalkonium chloride [68424-85-1] and benzethonium chloride (quaternary ammonium compounds) are allowed at 2 mg/L by FDA to disinfect water.

3.5. Water Treatment Compounds. Like the disinfecting agents, several water treatment compounds are used in aquaculture. Of particular interest ispotassium permanganate which is exempted from registration by EPA when used as an oxidizer or detoxifier and can control certain parasites, external bacteria, and possibly fungi (9).

3.6. Spawning Aids. One spawning aid is approved in the United States, human chorionic gonadotropin (Chorulon) (12). The drug is administered by intramuscular injection at 50-510 IU/lb body weight for males and 67-1816 IU/lb body weight for females.

3.7. Anesthetics. Tricaine methanesulfonate (MS-222) is the only currently approved anesthetic and requires a 21-day withdrawal time (10,12). The withdrawal time for MS-222 is of special concern to FDA when the broodfishes of salmon or other species are taken immediately after spawning for pet or human food. Both carbon dioxide and sodium bicarbonate [144-55-8] have also been used as anesthetics and are classified as unapproved drugs of Low Regulatory Priority by FDA; however, both chemicals are difficult to use with consistent results and involve long induction and recovery periods (9).

3.8. Herbicides. An array of herbicides is registered for use in aquatic sites, but copper sulfate and diquat dibromide are of particular interest because they also have therapeutic properties (9,10).Copper sulfate has been used to

control bacteria, fungi, and certain parasites, including *Ichthyophthirius* (ich). Diquat dibromide can control columnaris disease, but it also exhibits fungicidal properties (9)

3.9. Piscicides. The two piscicides, antimycin androtenone, are both used in ponds to control nuisance fish. Antimycin is used selectively to remove scaled fishes from catfish ponds, and rotenone is used as a general fish toxicant (9,10). Observations by catfish farmers indicate that antimycin at low concentrations also acts as a therapeutant against external parasites.

4. Regulation and Registration of Aquacultural Chemicals Outside the United States

The control of aquaculture drugs varies among countries from no regulation to restrictive regulations. Generally, few requirements are needed for a therapeutant to be licensed or registered in South America, Africa, and most of Asia. Seafood-exporting countries are increasingly concerned because importing countries may no longer accept products without a guarantee that the products contain no chemical residues of concern.

4.1. Canada. Except for environmental studies, requirements for registration data in Canada are similar to requirements in the United States. However, Canada has significantly different regulations and approval processes. Canadian aquaculturalists use drugs (Table 2) that are either licensed for other food animals and prescribed by veterinarians or used in an emergency under the direction of the Canadian Bureau of Veterinary Drugs (BVD) (13).

Table 2. **Chemicals Licensed for Use in Canadian Aquaculture**

Product (trade or alternative name)	CAS Registry Number	Molecular formula
Antibacterials		
florfenicol (Aquaflor)	[73231-34-2]	$C_{12}H_{14}Cl_2FNO_4S$
oxytetracycline[a] (Terramycin AQUA)	[79-57-2]	$C_{22}H_{24}N_2O_9$
sulfadimethoxine and ormetoprim[b]	[122-11-2]	$C_{12}H_{14}N_4O_4S$
(Romet-30 and Romet-B)	[6981-18-6]	$C_{14}H_{18}N_4O_2$
Sulfadiazine and trimethoprim	[68-35-9]	$C_{10}H_{10}N_4O_2S$
(Tribrissen)	[738-70-5]	$C_{14}H_{18}N_4O_3$
Disinfectants		
hydrogen peroxide	[7722-84-1]	H_2O_2
Antifungals/Antiparasiticides		
formalin (AquaLife Parasite – s)	[50-00-0]	CH_2O
Antiparasiticides		
azamethiphos (salmosan)		
Anesthetics		
metomidate (AquaLife marinil)		
tricaine methane sulfonate (AquaLife TMS powder)	[886-86-2]	$C_{10}H_{15}NO_5S$

[a] Licensed only for use in the treatment of fish and lobster. Withdrawal time is at least 40 d at >10°C and at least 80 d at <10°C.

[b] Withdrawal time is 42 d at >10°C and 81 d at <10°C.

The BVD is concerned about the lack of data on the pharmacokinetics of fishes, especially the difference in uptake of drugs at a range of temperatures (14). Chloramphenicol and tributyltin compounds are two classes of compounds that cannot be used in Canadian aquaculture. Canadian regulations also differ from the United States in that they have no minor-use policy or classifications such as Low Regulatory Priority drugs.

4.2. Europe. The European Agency for the Evaluation of Medicinal Products (EMEA) regulates the approvals of all Veterinary Medicinal Products in Europe and establishes the Maximum Residue Limit (MRL) for each animal drug (16). Those chemicals that should have established MRLs were banned from use if they were not established by January 1, 2000 (16). Requirements for MRLs for drugs are divided into four groups or annexes: Annex I = fixed MRL, Annex II = No MRL needed, Annex III = temporary MRL, and Annex IV = No MRL can be established (11). Banned from use are drugs such as the nitrofurans and chloramphenicol that have been placed in Annex IV. A MRL is required before a member country can evaluate a drug for approval. Although MRLs are European-wide, a license will depend upon the efforts of member countries and the drug sponsors (16). Under current regulations, veterinary medicines allowed for use in various European countries (Table (3)) are either fully licensed for aquacultural use (oxytetracycline, oxolinic acid) or can be prescribed by veterinarians if (1) the drugs are licensed for use on other food animals or in humans, (2) only a limited number of animals are treated, and (3) a 500 degree day withdrawal time is observed (16–19). Fish specific MRL approvals are available only for amoxicillin, potentiated sulfonamides, oxolinic acid, flumequine, sarafloxacin, oxytetracycline, and thiamphenicol (16).

4.3. Japan. In Japan, registration of drugs for aquatic species requires the same data as those required for drugs used on terrestrial animals. The Ministry of Agriculture, Forests, and Fisheries and the Ministry of Welfare control the use of chemicals in aquaculture in Japan (20). The preclinical data requirements include product chemistry, toxicity (acute, sub acute, special) using rats and mice, safety to target animals, and metabolism. The requirements for clinical data include availability and residues. As of April 2001, more chemicals were registered for aquacultural use in Japan than in any other country (Table 4).

4.4. Chile. The Servico Agricola y Ganadero has recently increased its scrutiny of drugs used in aquaculture. New approvals have and will become even more difficult. The agency will accept foreign data but some data are required to be generated in Chile. Table 5 lists the five drugs (i.e., antibacterials) currently approved in Chile (22). Other drugs being used or under consideration for approval include amoxicillin, benzocaine, chloramine-T, and MS-222.

4.5. Australia. In the past ten years, Australia has increased its aquaculture production and as a result has begun to register drugs and chemicals for that use. The National Registration Authority for Agricultural and Veterinary Chemicals has registered the following: benzocaine as a sedative and anesthetic for finfish and abalone, formalin to control protozoan and metazoan ectoparasites on fish and epicommensal ciliates on shrimp, flubendazole to control gill flukes on ornamental fish, leutinizing hormone releasing hormone analogue to induce spawning in finfish broodstock, methyltestosterone to produce female salmonid fish stocks, and trifluralin as a selective herbicide for prawn

Table 3. **Chemicals Authorized or Allowed for Use in Aquaculture in Certain European Countries**

Product (trade or alternative name)	CAS Registry Number	Molecular formula	Withdrawal time
		Antibacterials	
amoxicillin	[26787-78-0]	$C_{16}H_{19}N_3O_5S$	30–150 d[a]
florfenicol	[73231-34-2]	$C_{12}H_{14}Cl_2FNO_4S$	2 d in France
flumequine	[42835-25-6]	C14H12FNO3	2 d in France
oxolinic acid (Aqualinic Powder, etc)	[14698-29-4]	$C_{13}H_{11}NO_5$	6 d in France 500 ° d in UK[b]
oxytetracycline (Terramycin, etc)	[79-57-2]	$C_{22}H_{24}N_2O_9$	30–40 d at >9 or >10°C; 60 d at <9 or <10°C 400 degree d in UK[b]
sarafloxacin	[98105-99-8]	$C_{20}H_{17}F_2N_3O_3$	150° d
sulfadiazine	[68-35-9]	$C_{10}H_{10}N_4O_2S$	40 d at >10 − 12°C; 60–90 d at
and trimethoprim (Tribrissen, etc)	[738-70-5]	$C_{14}H_{18}N_4O_3$	<8 − 10°C 350–400 ° d in the UK[b]
sulfamerazine	[127-79-7]	$C_{11}H_{12}N_4O_2S$	30 d at>9°C; 60 d at 200 degree d in the UK[b]
sulfadimethoxine	[122-11-2]	$C_{12}H_{14}N_4O_4S$	49 d only in Germany
and trimethoprim	[738-70-5]	$C_{14}H_{18}N_4O_3$	
thiamphenicol	[15318-45-3]	$C_{12}H_{15}Cl_2NO_5S$	
		Topicals	
chloramine-T	[127-65-1]	$C_7H_7ClNNaO_2S$	
formalin	[50-00-0]	CH_2O	
azjamethiphos (Salmosan)			24 h
burserelin			
cypermethrin			100° d
diflubenzuron			Harest 2 years
emamectin (Slice)			
fenbendazole			
fearragillin	[23110-15-8]	$C_{26}H_{34}O_7$	500 ° d
hydrogen peroxide	[7722-84-1]	H_2O_2	24 h or none
praziquantel			
teflubenzuron			100° d
povidone–iodine compounds	[25655-41-8]		
sodium chloride	[7647-14-5]	NaCl	
trichlorfon	[52-68-6]	$C_4H_8C_{13}O_9P$	14–30 d
		Anesthetics	
chlorobutanol	[57-15-8]	$C_4H_7Cl_3O$	
carbon dioxide	[124-38-9]	CO_2	
tricaine methanesulfonate	[886-86-2]	$C_{10}H_{15}NO_5S$	
		Spawning Hormones	
Somatosalm			1 year

[a] Compounds used only in conjunction with other drugs.

[b] Degree days are number of days past treatment multiplied by the water temperature (°C).

Table 4. **Drugs Approved for Aquaculture Use in Japan, April 2001**[a]

Product	CAS Registry Number	Molecular formula	Use pattern, mg/kg per day[b]	Withdrawal time, d
		Antibacterials		
amoxicillin	[26787-78-0]	$C_{16}H_{19}N_3O_5S$	20–40	
ampicillin	[69-53-4]	$C_{16}H_{19}N_3O_4S$	5–20	5
bicozamycin benzoate				
doxycycline	[17086-28-1]	$C_{22}H_{24}N_2O_8H_2O$	20–50	20
erythromycin	[114-07-8]	$C_{37}H_{67}NO_{13}$	25–50	30
florfenicol	[73231-34-2]	$C_{12}H_{14}Cl_2FNO_4S$	10	
flumequine	[42835-25-6]	$C_{14}H_{12}FNO_3$	20	
josamycin	[16846-24-5]	$C_{42}H_{69}NO_{15}$	30–50	
leucomycin		$C_{42}H_{69}NO_{15}$		
lincomycin	[1392-21-8]	$C_{18}H_{34}N_2O_6S$	20–40	20
myroxacin				
nifurstylenic acid			50	2
novobiocin	[303-81-1]	$C_{31}H_{36}N_2O_{11}$	50	
oleandomycin	[3922-90-5]	$C_{35}H_{61}NO_{12}$	25	30
oxolinic acid	[14698-29-4]	$C_{13}H_{11}NO_5$	25–30d	14–30
oxytetracycline	[79-57-2]	$C_{22}H_{24}N_2O_9$	50	25–30
phosphomycin calcium				
spiramycin	[8025-81-8]	$C_{43}H_{74}N_2O_{14}$	25–40	30
sulfadimethoxine	[122-11-2]	$C_{12}H_{14}N_4O_4S$	50–100	30
sulfamonomethoxine	[1220-83-3]	$C_{11}H_{12}N_4O_3S$	100–200	15–30
sulfamonomethoxine and ormetoprim	[1220-83-3] [6981-18-6]	$C_{11}H_{12}N_4O_3S$ $C_{14}H_{18}N_4O_2$	10–20	15
sulfisozole	[73247-57-1]		100–200	10–15
tetracycline	[60-54-8]	$C_{22}H_{24}N_2O_8$	55–110	10
thiamphenicol	[15318-45-3]	$C_{12}H_{15}Cl_2NO_5S$	20–50	15
tobicillin				
		Anesthetics		
eugenol	[97-53-0]	$C_{10}H_{12}O_2$	20–50c	
		Paracite repellants		
hydrogen peroxide	[7722-84-1]	H_2O_2		
lysozyme	[9001-63-2]			
praziquantel	[55268-74-1]	$C_{19}H_{24}N_2O_2$		
		Disinfectants		
povidone–iodine compounds	[25655-41-8]			
trichlorfon	[52-68-6]	$C_4H_8Cl_3O_4P$	0.2–0.3c	5

[a] Ref. 21.
[b] Unless otherwise noted.
[c] mg/L solution.
[d] 25–30 mg/kg per day or 5–10 mg/L.

larvae mycosis (see Table 6 for details). Certain chemicals have been exempted from the need for registration: calcium carbonate [471-34-1], $CaCO_3$; calcium hydroxide [1305-62-0], $Ca(OH)_2$; calcium oxide [1305-78-8], CaO; magnesium carbonate; calcium sulfate [7778-18-9], CaO_4S; zeolite [1318-02-1], $Na_2O{\cdot}Al_2O_3.(SiO_2)X.(H_2O)Y$; aluminum sulfate [10043-01-3], $Al_2O_{12}S_3$; ferric chloride [7705-08-0], Cl_3Fe; and inorganic and organic fertilizers (11,23).

Table 5. **Antibacterials Approved for Aquaculture Use in Chile**[a]

Product	CAS Registry Number	Molecular formula
florfenicol	[73231-34-2]	$C_{12}H_{14}Cl_2FNO_4S$
flumequine	[42835-25-6]	$C_{14}H_{12}FNO_3$
oxolinic acid	[14698-29-4]	$C_{13}H_{11}NO_5$
oxytetracycline	[79-57-2]	$C_{22}H_{24}N_2O_9$
sarafloxacin	[98105-99-8]	$C_{20}H_{17}F_9N_3O_3$

[a] Ref. 22.

Table 6. **Chemicals Registered for Aquaculture Use in Australia**[a]

Product	CAS Registry Number	Molecular formula
benzocaine	[94-09-7]	$C_9H_{11}NO_2$
formalin	[50-00-0]	CH_2O
flubendazole		
leutinizing hormone releasing hormone analogue		
methyltestosterone	[58-18-4]	$C_{25}H_{38}O_2$
trifluralin	[1582-09-8]	$C_{13}H_{16}F_3N_3O_4$

[a] Ref. 23.

5. Promising Chemicals for Registration for Aquaculture

More therapeutants and vaccines may soon be added to the medicine chest of fish farmers. A variety of chemicals have potential for registration and use in aquaculture (9,11,24,25).

5.1. Antibacterials. Research has been conducted on three important external and systemic antibacterial compounds in the United States. Various registration data are or have been generated by the U.S. Geological Survey's Upper Midwest Environmental Sciences Center at La Crosse, Wisconsin (UMESC), and USFWS on chloramine-T with funds from the Federal-State Aquaculture Drug Approval Partnership (a project of the International Association of Fish and Wildlife Agencies = IAFWA Project) (26–28). Chloramine-T is used mainly to control bacterial gill disease on fry and fingerlings of salmonids but is effective for other external bacterial diseases of a variety of fishes (9,25,28). (see CHLORAMINES AND BROMAMINES). Hydrogen peroxide was identified by UMESC as a good candidate to control external bacterial infections on all fish. Research is underway at UMESC with funds from the IAFWA Project to complete the technical sections needed for approval (9,28). Efforts by UMESC and USFWS with funds from the IAFWA Project should allow the expansion and extension of oxytetracycline to other fish species and other diseases (9,28).

Sarafloxacin [98105-99-8], $C_{20}H_{17}F_2N_3O_3$, a broad-spectrum antibacterial in a class of compounds called fluoroquinolones, was under development by Abbott Laboratories (Chicago, Ill.) for worldwide use by the aquaculture industry until the U.S. Centers for Disease Control and Prevention (CDC) presented

concerns about the use of all fluoroquinolones in animal health because of the perceived potential for developing pathogen resistance to drugs used in humans. It is doubtful that CVM will allow any approvals for sarafloxacin or any fluoroquinolone (e.g., enrofloxacin) for aquaculture uses (9,28). (see ANTI-BACTERIAL AGENTS, SYNTHETIC, QUINOLONES).

The University of Idaho and USFWS, with funds from the Bonneville Power Administration, was also gathering data for registration of erythromycin when CDC also became concerned about the use of any human drug in animals because of antimicrobial resistance concerns. Erythromycin is intended for control of bacterial kidney disease in salmonid fingerlings that can also be transmitted by broodstock to the eggs (9). It is not known if this approval will ever be completed (see ANTIBIOTICS, MACROLIDES).

Florfenicol, an oral antibacterial is being considered for development in the United States by the sponsor for use on catfish and salmonids. Efforts are underway through a grant from the Multi-State Conservation Grant Program to generate efficacy data on other species and other diseases on florfenicol by USFWS and UMESC (28). Amoxicillin is another antibacterial that has potential for development for control of streptococcal infections in tilapia and hybrid striped bass (9).

5.2. Fungicides and Parasiticides. UMESC is working on several fronts to improve the availability of fungicides and parasiticides. UMESC, with funding from Bonneville Power Administration screened and tested promising candidates for replacement of malachite green as both fungicides and parasiticides (9). Although several compounds show promise for controlling fungi, the best fungicide candidate was identified as hydrogen peroxide. UMESC has developed data with funds from the IAFWA Project to gain an approval for use of hydrogen peroxide to control fungal infections on all fish and their eggs. Hydrogen peroxide was also identified by UMESC as a good candidate to control external parasitic infestations on all fish. Research is underway at UMESC with funds from the IAFWA Project to complete the technical sections needed for approval. Pyceze is another candidate fungicide that was identified in the United Kingdom and is now being developed worldwide by the sponsor (9).

The approval of formalin as a fungicide now extends to all fish eggs and may soon extend to all fish. The approval of formalin as a parasiticide was also extended through efforts by UMESC with funds from the IAFWA Project and efforts by Auburn University with funds from the National Research and Support Program Number Seven (28).

The Harry K. Dupree Stuttgart National Aquaculture Research Center, Stuttgart, Arkansas (SNARC) has developed data on copper sulfate with funds from the IAFWA Project for the control of *Ichthophthirius*, an external protozoan that causes significant losses in the catfish industry. Potassium permanganate is another chemical being researched at SNARC with funding from the IAFWA Project for use as a control for *Ichthyophthirius* (28). Other promising parasiticides include praziquantel, fumagillin, and sea lice control agents (e.g., azamethiphos, cypermethrin, emamectin, and hydrogen peroxide) (9). (See ANTIPARASITIC AGENTS, ANTHELMINTICS).

5.3. Disinfectants. Promising disinfectants include ultraviolet (uv) light andozone [10028-15-6], O_3. High doses of uv light have prevented the transmission

of the epizootic epitheliotropic virus (EEV) disease among lake trout (*Salvelinus namaycush*) (25). Uv sterilization can only be successful when water volumes and suspended solids are low (29). Ozone is also considered to be a good candidate to both control EEV and other diseases, and remove chemicals and wastes from aquacultural effluents (25). However, ozone is considered to be a food additive by FDA and, therefore, must meet registration requirements that are almost as stringent as the registration requirements for drugs.

5.4. Anesthetics. Ethyl aminobenzoate [94-09-7] (benzocaine), $C_9H_{11}NO_2$, was a candidate anesthetic but it would have required additional mammalian safety studies, did not have a sponsor, and probably would not have allowed the use of spawned-out broodstock carcasses to be used for pet or human food. AQUI-S, an anesthetic developed in New Zealand has great potential as a zero withdrawal drug and is being developed by its sponsor for worldwide approval. In the United States, UMESC with funds from the IAFWA Project is developing the anesthetic for use on all fish (9,28). Electronarcosis is an alternative to chemical anesthesia that uses varying electrical frequencies to rapidly anesthetize fishes and allow gentle recovery. Electronarcosis has been used effectively on tilapia (*Oreochromis* sp.) and common carp (*Cyprinus carpio*) and the technique is being tested with other fishes (30,31).

5.5. Herbicides and Piscicides. Registrants reregistered aquatic herbicides under the 1988 Pesticide Law in the United States. Reregistration of piscicides was funded mainly by public agencies. Data collection for the reregistration of rotenone was completed by UMESC. Antimycin must be reregistered soon but funds have not been available to complete the data requirements and it may be suspended or canceled if the data are not generated soon. Control of Bayluscide (niclosamide) was transferred from the Mobay Corp. (now Bayer Corporation) to USFWS after Mobay determined that the estimated $2.5–3.5 million for reregistration was not economically feasible. Bayluscide is used by USFWS to control the sea lamprey (*Petromyzon marinus*) in the Laurentian Great Lakes and to manage and control nuisance mollusks in both aquaculture and natural waters. Bayluscide also has the potential to control digenetic trematodes of finfishes and snail vectors of several parasites, including *Bolbophorus* sp. (25,32).

BIBLIOGRAPHY

"Aquaculture," in *ECT* 3rd ed., Vol. 3, pp. 194–213, H. P. Clemens and M. Conway, University of Oklahoma; in *ECT* 4th ed., Vol. 3, pp. 608–623, by Rosalie A. Schnick, U. S. Fish and Wildlife Science; "Aquaculture Chemicals" in *ECT* (online), posting date: December 4, 2000, by Robert Stickey, Texas A & M University.

CITED PUBLICATIONS

1. R. A. Busch, *Vet. Hum. Toxicol.* **29**(Suppl. 1), 45 (1987).
2. L. W. Harrell, *Vet. Hum. Toxicol.* **29**(Suppl. 1), 49 (1987).

3. M. H. Beleau and J. A. Plumb, *Vet. Hum. Toxicol.* **29**(Suppl. 1), 52 (1987).
4. J. P. McCraren, *The Aquaculture of Striped Bass*, Sea Grant Publication No. UM-SG-MAP-84-01, University of Maryland, College Park, Md., 1984.
5. G. Lio-Po in J. V. Juario, R. P. Ferraris, and L. V. Benitz, eds., *Proceedings of the Second International Milkfish Aquaculture Conference, October 4–6, 1983*, Iloilo City, Philippines, 1984.
6. C. Brown, *Vet. Hum. Toxicol.* **29**(Suppl. 1), 35 (1987).
7. R. R. Williams and D. V. Lightner, *J. World Aquacult. Soc.* **19**, 188 (1988).
8. C. J. Sindermann and D. V. Lightner, *Disease Diagnosis and Control in North American Marine Aquaculture*, Elsevier, New York, 1988.
9. R. A. Schnick, *Use of Chemicals in Fish Culture: Past and Future*, Chapt. 1, pp. 1–14 *in* D. J. Smith, W. H. Gingerich, and M. G. Beconi-Barker, eds., Xenobiotics in Fish, Kluwer Academic/Plenum Publishing Corp., New York, 1999.
10. Joint Subcommittee on Aquaculture, *Guide to Drug, Vaccine, and Pesticide Use in Aquaculture*, Texas Agricultural Extension Service, College Station, Tex., 1994.
11. R. A. Schnick, and co-workers *Bull. Euro. Assoc. Fish Path.* **17**, 251 (1997).
12. U. S. Food and Drug Administration (FDA), *Food and Drugs, Code Fed. Reg.* **21**, Parts 500–599 (2000).
13. G. E. Brooks, *Aquacult. Assoc. Canada Bull.* **89–4**, 39 (1989).
14. G. R. Johnson and D. J. Rainnie, *Aquacult. Assoc. Canada Bull.* **89–4**, 43 (1987).
15. R. Linehan, personal communication, April 2001.
16. D. J. Alderman, personal communication, April 2001.
17. J. Shepherd, paper presented to the *Aquaculture Feed and Veterinary Products: Worldwide Business Opportunities for Feed, Pharmaceutical, and Chemical Companies Conference*, Stamford, Conn., June 6–8, 1990.
18. L. A. Brown, *Vet. Hum. Toxicol.* **29**(Suppl. 1), 54 (1987).
19. E.-M. Bernoth, *J. Vet. Med. Ser. B.* **37**, 401 (1990).
20. T. Sano and H. Fukuda, *Aquaculture* **67**, 59 (1987).
21. S. Ishihara, personal communication, April 2001.
22. D. Farcas, personal communication, April 2001.
23. K. Allan, personal communication, April 2001.
24. D. J. Alderman in J. F. Muir and R. J. Roberts, eds., *Recent Advances in Aquaculture*, Vol. 3, Timber Press, Portland, Oreg., 1988, p. 1.
25. F. P. Meyer and R. A. Schnick, *Rev. Aquat. Sci.* **1**, 693 (1989).
26. R. A. Schnick, *Trans. 61st No. Am. Wildlife Nat. Res. Conf.* **61**, 6 (1996).
27. R. A. Schnick, W. H. Gingerich, and K. H. Koltes, *Fisheries* **21**(5), 4 (1996).
28. B. R. Griffin, R. A. Schnick, and W. H. Gingerich, *Aquacult. Mag.* **26** (3), 56 (2000).
29. G. Barnabe', *Aquaculture*, Vol. **1**, Ellis Horwood, London, UK, 1990.
30. W. T. Barham, A. J. Schoonbee, and J. G. J. Visser, *Onderstepoort J. Vet. Res.* **54**, 617 (1987).
31. *Ibid.*, **56**, 215 (1989).
32. B. R. Griffin, personal communication, May 2001.

ROSALIE A. SCHNICK
Aquaculture Chemicals