THE APPROACHING CRISIS IN THE REGISTRATION OF FISHERY CHEMICALS

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ABSTRACT

Review of the status of chemicals used in fisheries indicates that many lack proper registrations. Regulations of the U.S. Environmental Protection Agency and U.S. Food and Drug Administration require that all existing registrations be reviewed and reregistered by October 1977. Adequate data to support reregistration are lacking for some of the most widely used chemicals. Applications of unregistered compounds are strictly prohibited under penalty of law.

Cancellation of existing registrations, high costs of research, high manpower requirements, and the long time required to complete adequate research contribute to a situation in which fishery workers may be deprived of needed management tools.

All phases of fishery management are directly affected. The loss of therapeutants, anesthetics, herbicides, and piscicides will be reflected in lower hatchery production, fish of poorer quality,—and increased costs. Survival of fish that are in poor health when stocked will be reduced. Loss of the use of chemicals to reclaim or renovate lakes and streams will further reduce the success of stocking programs and increase management costs. Commercial producers may be unable to cope with disease and water quality problems. Researchers will be unable to maintain experimental animals in consistently uniform health or to obtain high quality stock without significant increases in cost.

A significant increase in funding and research by Federal, State, and industrial agencies is required if the crisis is to be avoided.

The regulation of chemical applications in the environment is surrounded by confusing questions about which fishery chemicals are registered, which analogs of given compounds are approved for aquatic applications, and what use patterns are permitted. Congress charged the U.S. Environmental Protection Agency (EPA) with control of the use of pesticides and the U.S. Food and Drug Administration (FDA) with the control of the use of drugs, and left the promulgation of rules and guidelines to these respective agencies.

The agencies were overwhelmed by the assignment of new responsibilities and deadlines, the diversity of the environments in which the chemicals were to be used, the multitude of formulations and use patterns, and legal complications. As a result, progress in the development of rules and guidelines has been slow, and action on registration applications has been delayed.

The authority for EPA to control pesticides was provided by the Federal Insecticide, Fungicide, and Rodenticide Act of 1964, the National Environmental Policy Act of 1969, and the Federal Environmental Pesticide Control Act (FEPCA) of 1972. The FDA authority was provided in the Federal Food, Drug, and Cosmetic Act passed in 1938 and amended in 1967, 1969, and 1972 (Cumming 1975).

The proposed *Guidelines for Registering Pesticides* were not published until 25 June 1975 and the *Requirements for Registration of Pesticides* until 3 July 1975 (EPA 1975a and b). Furthermore, all pesticides registered before 4 August 1975 must be reregistered by 21 October 1977. A total of 29,000 pesticides formulated with 1,500 active ingredients are involved in the reregistration requirement (Anonymous 1976c). Regulatory authority now covers all activities that introduce or provide for the introduction of pesticides or drugs into natural surface water systems, culture systems, or the feed of cultured organisms (U.S. Congress 1969).

Chemicals employed in situations other than natural waters must be prevented from entering the aquatic environment, either by holding treated water until the compound has been degraded to nontoxic substances by natural forces or by chemical detoxifiers, or selectively removed by filtration through appropriate absorbents or adsorbents.

Regulatory control covers all facets of development, distribution, and use: manufacturing process, bulk shipment, formulation, retail packaging, labeling, interstate shipment, applicators, application rates, use patterns, and species on which the compound can legally be applied (EPA 1976a). All producers, handlers, and applicators can thus be held legally accountable if they misuse a pesticide. Only uses described on the label are permitted, and only at the rates listed. Applications at less than or more than the approved rate are equally illegal.

A review of the chemicals used in fish culture and fishery management indicates that many have never been properly registered, even though some, such as formalin, have been in use for over 100 years. As of 1 February 1976, only 18 compounds were registered for fishery use and only 10 of these for use on fish used for human food (Meyer et al. 1976; Table 1). The FDA employs two categories, "food fish" and "nonfood fish," in determining which fishery use patterns are to be permitted. Food fish are those that may be consumed by man—species such as trout, catfish, bass, and bluegills. Regulations cover applications to all life stages (eggs, fry, fingerlings, subadults, and broodfish). "Nonfood fish" are bait and ornamental fishes such as golden shiners, fathead minnows, and the many species reared by aquarists. Fish used for research fall in either category, depending on their food or nonfood designation. Thus, test goldfish can be treated with Masoten®, but test catfish bluegills and salmon cannot.

Although extensive testing is required for both food and nonfood fish, additional data on metabolites, residues, and residue persistence must be submitted for establishment of a minimum tolerance for chemicals applied to food fish.

Chemicals registered for use on food fish include copper sulfate, Finquel®, 2,4-D, diquat dibromide, endothall, lime, sodium chloride, simazine, sulfamerazine, and Terramycin®. Compounds registered for use on nonfood fishes are antimycin, rotenone, Bayer 73, 3-trifluoromethyl-4-nitrophenol (TFM), the combination of TFM and Bayer 73, Masoten, Casoron®, and Furanace® (Meyer et al. 1976).

As the review of current drug and pesticide registrations by both EPA and FDA proceeds, many of the applications now permitted will not be continued. Most fishery uses of chemicals constitute "minor use"; consequently, industry will not be able to justify the

Table 1. Summary of registration status (R = registered; U = unregistered) of fishery chemicals, February 1976 (from Meyer et al. 1976).

Compound and Use	*Registration Status*	*Special Conditions*	*Comments*
Piscicides			
Antimycin [Fintrol®]	R	Nonfood use only	Major obstacle to food use registration is the lack of an analytical method to determine possible residues in fish and the environment.
GD-174 [2-(digeranylamino)-ethanol]	U	—	Strictly experimental, research under way.
Rotenone [Noxfish®, Pronoxfish®, Chem-Fish Regular®, etc.	R	Nonfood use only	Label amended in December 1975 to permit use of higher rates under special conditions. See label for approved uses.
Squoxin [1, 1' - methylenedi -2-naphthol]	U	—	Sponsorship assumed by National Marine Fisheries Service in 1975; submitted IR-4 for review.

Compound and Use	Registration Status	Special Conditions	Comments
Lampricides			
Bayer 73 [Bayluscide®]	R	Nonfood use and only by Great Lakes Fishery Commission (GLFC), Federal, or State personnel	Used as survey tool to check abundance of lamprey larvae. Research under way toward registered use as lampricide.
TFM [3-trifluoromethyl-4-nitrophenol]	R	Nonfood use and only by GLFC, Federal, or State personnel	Submission filed with EPA in February 1976 for amendment of registration and Petition for Exemption from Tolerance (PET). Use presently permitted on an annual basis pending review of latest submission.
TFM: Bayluscide mixture	R	Nonfood use and only by GLFC, Federal, or State personnel	See comments on TFM and Bayluscide.
Collecting Aid			
Isobornyl thiocyanoacetate [Thanite®]	U	—	Thanite is registered as an insecticide. Compound is in developmental stage for fishery use, still strictly experimental; Experimental Use Permit (EUP) requested.
Anesthetics			
MS-222 [Finquel®]	R	Includes use with food fish	21-day withdrawal period required.
MS-222: quinaldine sulfate mixture [Finstill]	U	—	Awaiting ruling by FDA on submission for registration; still experimental February 1976.
Quinaldine sulfate [2-methylquinoline sulfate]	U	—	Awaiting ruling by FDA on submission for registration; still experimental February 1976.
Parasiticides			
Formalin [Formaldehyde solution]	U	—	Awaiting ruling by EPA on petition for exemption from registration and by FDA on submission of Not New Drug Monograph.
Formalin: malachite green mixture	U	—	Research under way.
Malachite green oxalate	U	—	Research under way.
Trichlorfon [Masoten®]	R	Nonfood use only	No known research under way.

Compound and Use	Registration Status	Special Conditions	Comments
Osmoregulatory Enhancer			
Salt [sodium chloride]	R	Includes use with food fish	Declared Generally Regarded as Safe (GRAS) by EPA.
Antibacterial Drugs			
Furazolidone [NF-180® Furoxone®]	U	—	No known research under way.
Nifurpirinol [Furanace®]	R	Nonfood use only	Submission on food fish use will be forwarded in spring 1976.
Nitrofurazone [nfz®, Furacin®]	U	—	No known research under way.
Oxytetracycline [Terramycin®]	R	Includes use with food fish	See label for species and withdrawal times required. Has tolerance of 0.1 ppm in edible tissues of salmonids and catfish.
Sulfamerazine [N^1 – (4-methyl-2-pyrimidyl) sulfanilamide]	R	Includes use with food fish	See label for species and withdrawal times required. Has zero tolerance in edible tissues of trout.
Disinfectants			
Calcium hypochlorite [HTH®]	U	—	Registered for use in swimming pools. Industrial sponsor resubmitted application for fishery use registration to EPA in February 1976.
Hyamine 1622	U	—	Research terminated.
Povidone-iodine [Betadine®]	U	—	Registered for use on human and animal skin but not fish; industrial sponsor ready to submit New Animal Drug Application (NADA) to FDA.
Herbicides			
Copper sulfate [Cutrine®, Algimycin®, K-Lox®, Komeen®, etc.]	R	Includes use with food fish	Consult label for limitations. Tolerance of 1 ppm in potable water and Exemption from Tolerance in fish for copper sulfate, basic copper carbonate, and copper triethanolamine.
Dichlobenil [Casoron®]	R	Nonfood use only	Consult label for limitations. No known research under way.
DMA-2, 4-D [Dimethylamine salt of	R	Includes food fish use but only by	Consult label for limitations. Tolerance in raw fish and

Compound and Use	*Registration Status*	*Special Conditions*	*Comments*
(2,4-dichlorophenoxy) acetic acid]		Federal, state or local public agencies	shellfish is 1 ppm.
Diquat dibromide [Diquat Water Weed Killer®, Diquat 2 Spray®]	R	Includes use with food fish	Consult label for limitations. Interim tolerance in potable water set at 0.01 ppm.
Diuron [Karmex®]	U	—	No research under way; submitted to IR-4 for review.
Endothall [Aquathol®, Hydrothol®, Hydout®, Q-Dril®, etc.]	R	Includes use with food fish	Consult label for limitations. Interim tolerance of 0.2 ppm in potable water.
Simazine [Aquazine®]	R	Includes use with food fish	Consult label for limitations. Tolerances set at 12 ppm in raw fish and 0.01 ppm in potable waters.
Oxidizing Agent			
Potassium permanganate [Cairox®]	U	—	Awaiting ruling by EPA on petition that use as oxidizing agent does not constitute classification of the chemical as a pesticide.
Pond Sterilant			
Lime [Calcium hydroxide]	R	Includes use with food fish	Declared Generally Regarded as Safe (GRAS) by EPA.

Table 2. Required toxicity studies to support submissions for the new registration of chemical uses†

I. Hazards to humans and domestic animals

A. Acute

1. Acute oral LD50—rat
2. Acute dermal LC50—rabbit
3. Acute primary dermal irritation—rabbit
4. Acute primary eye irritation—rabbit

*5. Inhalation LD50—rat

*6. IV or IP injections

B. Subacute

*1. 21-day subacute dermal—rabbit

*2. 14-day subacute inhalation—rat

*3. 90-day subacute oral—rat and hamster

*4. Teratology—rabbit

*5. Neurotoxicity—adult hen and rat or dog

*6. Metabolism—cow or chicken and rat or dog

Table 2. (Continued) Required toxicity studies to support submissions for the new registration of chemical uses†

C. Chronic

*1. 2-year oncogenicity—rat and mouse or hamster
*2. 6-month feeding—dog
*3. Three-generation reproduction—rat
*4. Other chronic tests—hematopoiesis, endocrine, or histopathology

D. Special studies

*1. Mutagenicity—in vivo cytogenetics, heritable translocation test, and specific locus test
*2. Potentiation—if there is a possibility that the toxic effects of the chemical could be potentiated, studies are required
*3. Foliar residue—studies for persons reentering treated area
*4. Other studies—when appropriate, additional studies based on similarity of the chemical structure between the test compound and those known to produce specific toxic effects may be required. Studies may also be required to determine reversibility of effects found after subacute feeding

II. Hazards to fish and wildlife

A. Acute

1. Avian acute oral LD50—mallard and bobwhite quail or ringnecked pheasant
2. Fish acute toxicity 96-h LC50—rainbow trout and bluegill
3. Invertebrate acute toxicity 96-h LC50—*Daphnia*
*4. Mammalian toxicity data—as required for evaluation hazard to humans and domestic animals—will normally be adequate to indicate hazard to wild animals
*5. Acute toxicity data 96-h LC50—shrimp and crabs
*6. Acute toxicity data 96-h LC50—oyster larvae
*7. Toxicity and residue—bottom-feeding fish, coldwater and warmwater fish predators, mollusks, crustaceans, insect larvae or nymphs

B. Subacute

1. 8-day avian subacute dietary LD50—mallard
*2. Mammalian toxicity data—as required for evaluating hazard to human and domestic animals will normally be adequate to indicate hazard to wild mammals
*3. Toxicity and residue—bottom-feeding fish, coldwater and warmwater fish predators, mollusks, crustaceans, insect larvae or nymphs

C. Chronic

*1. One-generation reproduction—bobwhite or mallard
*2. Subacute or chronic fish and/or invertebrate reproduction—fish, 1 year; invertebrate, 3 months.

D. Special studies

*1. Field tests—as needed
*2. Toxicity data—as needed
*3. Tolerance establishment—if chemical will be used on food fish

† Excerpted from EPA (1975a).

* Optional tests which may be required by the regulatory agencies if the use pattern is likely to create an unusual or unique potential hazard to applicators or nontarget organisms, if the nature of the chemical suggests potential hazards, or if required tests indicate unusual side effects.

sizable expenditures needed to develop the data required for continued registration. In addition, as testing and research on drugs and pesticides continue, it must be expected that the registrations of some approved compounds will be cancelled or withdrawn on the basis of the results of that research. Such action is frequently related to the discovery of carcinogenic or teratogenic properties (FDA 1976).

The reregistration schedule established by EPA directly affects chemicals registered for fishery use. Copper sulfate and 2,4-D should be ready for full reregistration because all requested data are available. Those considered ready for conditional reregistrations (but lacking long-term testing data) include Bayer 73, Casoron, rotenone (cube resins, derris resins, dihydrorotenone), diquat dibromide, endothall, and simazine. Registered fishery chemicals which have not been assessed include acetic acid, antimycin, sodium chloride, Terramycin, and TFM (EPA 1976b).

Pesticides that EPA considers to be too dangerous to use because of their unreasonable adverse effects are subject to Rebuttable Presumptions Against Reregistration (RPAR), an action which EPA has started on compounds such as Kepone and endrin. The RPAR may be removed if evidence can be presented showing that no hazard exists or that the risk can be reduced to such an extent that significant adverse effects are unlikely. Also, EPA may decide not to cancel a pesticide if it can be shown that the benefits far exceed the risks (EPA 1976b). Fishery chemicals which are candidates for this consideration include Masoten, piperonyl butoxide (a synergist), and rotenone (Anonymous 1976a and b).

The problem of shrinking options also extends to drug applications. FDA recently published a notice of intent to cancel registrations of furazolidone (NF-180®) for veterinary uses, and to carefully study four other nitrofurans—including nitrofurazone—because of possible carcinogenicity or mutagenicity. Loss of furazolidone and nitrofurazone as potential controls for bacterial fish diseases would create a serious void in the fish culturists' medicine chest. Currently, only Terramycin and sulfamerazine

Table 3. Studies required to support applications for the reregistration of chemical uses†

If the toxicity testing data previously submitted to EPA conforms to the requirements of the Guidelines, no acute toxicity testing for evaluation of hazards to man are required for reregistering pesticides that are currently registered with EPA.

I. Hazards to humans and domestic animals
   - *A. Teratogenicity—rabbit
   - *B. 2-year oncogenicity—rat, mouse and/or hamster
   - *C. Mutagenicity—in vivo cytogenetics, heritable translocation test, and specific locus test
   - *D. Chronic feeding tests—central nervous system, hematopoietic system, histological changes in the liver, kidney, and reproductive systems
   - *E. Three-generation reproductive studies—rat
   - *F. Foliar residue—studies for persons reentering treated area

II. Hazards to fish and wildlife
   - A. Avian subacute dietary LC50—8-day protocol
   - B. Acute toxicity 96-h LC50—fish
   - C. Acute toxicity 96-h LC50—invertebrate

† Excerpted from EPA (1975a).

* Optional tests which may be required by the regulatory agencies if the use pattern is likely to create an unusual or unique potential hazard to applicators or nontarget organisms, if the nature of the chemical suggests potential hazards, or if required tests indicate unusual side effects.

are available as registered antibacterials. Furnace, also a nitrofuran, is the only potential replacement candidate at this time.

The number of fishery chemicals which are not registered or are not adequately registered also poses a serious predicament. As previously mentioned, 8 of the 18 compounds registered for fishery use are registered only for use on nonfood fish; and 5 experimental chemicals and 10 chemicals now widely applied in fish culture, management, or research are not registered for any fishery use.

Submissions have been made to the regulatory agencies concerning formalin, quinaldine sulfate, a mixture of quinaldine sulfate and MS-222, malachite green, calcium hypochlorite, and Thanite®. Until questions have been resolved and additional research is completed, however, it is unlikely that any of these compounds will be registered.

Several chemicals already registered for other uses, and currently being used by fishery workers without proper approvals, are being reviewed by EPA. Calcium hypochlorite should be ready for full registration as an antimicrobial in other than fishery uses. Diuron (a terrestrial herbicide) and Thanite (an insecticide) are considered ready for conditional registrations. Formaldehyde, which is registered as a fungicide and antimicrobial in agriculture, is not considered ready for reregistration. Other chemicals used by fishery workers which have not been adequately assessed include Betadine®, malachite green, methylene blue, and potassium permanganate.

What then is the picture regarding the registration of fishery chemicals? First of all, it should be noted that the registration situation is not unique to the fishery field. All facets of chemical use face the same situation, whether in agriculture, forestry, or other fields of human endeavor. The "grandfather clause," to which many users wishfully refer, has long since been superseded by new and more restrictive requirements. Warnings issued by Lennon (1967), Meyer (1971), and others are proving valid. Clarifications of regulatory authority and enforcement have developed slowly. The deliberate pace at which regulatory control has come to pass lulled some industries and managers into the false assumption that the use of chemicals in fisheries is too minor to attract attention from the EPA and FDA. This definitely is not true. Each clarification of guidelines and requirements has led to more stringent controls. Federal and State agencies are no longer granted immunity to Federal regulations. In fact, such agencies are now expected to lead the way in complying with regulatory control of drug and pesticide uses. In short, the application of any chemical by anyone for purposes other than those specified on the label is illegal. The use of unlabeled chemicals for nonregistered purposes is of course also prohibited.

Penalties for noncompliance will be assessed according to individual situations. Anyone (registrant, commercial applicator, wholesaler, dealer, retailer, or distributor) found in violation of the provision of FEPCA will be assessed a civil penalty of not more than $5,000 by the Administrator of the EPA after due notice has been given. In addition, anyone who knowingly violates the Act shall be guilty of a misdemeanor, and on conviction may be fined not more than $25,000, or imprisoned for not more than 1 year, or both. Likewise, any private applicator or other person not included in the preceding provisions who violates FEPCA shall be subject to a civil penalty of not more than $1,000, and on conviction for a deliberate violation may be fined not more than $1,000, or imprisoned for not more than 30 days, or both. All Federal and State agencies are subject to all provisions of the Act, unless emergency conditions are determined to exist by the EPA Administrator (U.S. Congress 1972).

Most efforts to register chemicals for fishery use are now centered in, or related to, Federal agencies. In the U.S. Department of the Interior, the Fish and Wildlife Service has charged the Fish Control Laboratory, La Crosse, Wisconsin, with primary responsibility for efforts toward registration of fishery compounds. Work related to the registration of herbicides has been assigned to the Fish Pesticide Research Laboratory, Columbia, Missouri.

A submission for registration must include adequate data to prove that a chemical is effective for the intended function without unreasonable adverse effects on the environment; that the compound has no teratogenic, oncogenic, or mutagenic properties; and that recommended use patterns will leave no harmful residues in animal tissues or the

environment. In addition, data must be provided on the persistence of the compound, its rate of degradation, possible degradation products and their potential effects, and methods to counteract the chemical or otherwise remove it from treated waters.

The research needed to develop the data required for the support of an application for registration or reregistration are listed in Tables 2 and 3. Because of the specialized facilities required for mammalian safety studies, most such research must be largely contracted to firms that specialize in conducting work of this nature. The costs of such studies are very high—about $250,000 for a total safety evaluation. Since not all compounds require a complete evaluation, some may cost no more than $100,000.

Mammalian safety studies represent only one of the types of studies that require sizable expenditures of time and money. When other safety studies, efficacy tests, chemical characterization, and metabolic studies are included, the cost of developing a new compound may reach $12 to $14 million. The time required for completion is 8 to 10 years (Lewert 1976). As a result, any urgently needed chemical that is cancelled or cannot be reregistered could not be quickly replaced.

DISCUSSION

Although no single regulation or piece of legislation on the use of fishery chemicals has created a major problem, the collective effect of the several individual actions will have a major impact. All registrations must now be considered suspect. Those which lack adequate supporting data will not be renewed. Many fishery chemicals now registered are in this category. The high cost of generating required data will limit the amount of effort industry or the Federal Government can expend. It is a hard fact that not all uses can be adequately researched to provide an effective defense. Time constraints also work against development of a successful defense.

Although registered chemicals exist for most needs—i.e., parasiticides, antibacterials, anesthetics, herbicides, and piscicides—only one or two compounds are available in each category. The loss of a single approval could create a major void in an area of critical need, with little or no chance of having a replacement in the near future. Evidence now in hand suggests that this situation is likely to develop.

The continued erosion of justification for chemical uses will soon reach a critical stage. It is often assumed that chemical applications currently used routinely will continue to be used. This will not be permitted under the existing regulations. *Every* use that is not properly registered will be denied.

All phases of fishery management are directly affected. The loss of therapeutants, anesthetics, herbicides, and piscicides will be reflected in lower hatchery production, fish of poorer quality, lower post-stocking survival, and increased costs. Loss of the use of chemicals to reclaim or renovate lakes and streams will further reduce the success of stocking programs and increase management costs. Commercial producers may be unable to cope with disease and water quality problems. Researchers will be unable to maintain experimental animals in consistently uniform health or to obtain high quality stock without significant increases in cost.

The approaching crisis was not without adequate warnings. Inadequate funding, limited laboratory facilities, a shortage of manpower, and the failure of management officials to recognize the implications of developing EPA and FDA controls has placed fishery workers in a critical situation. Relief can only come about through a combined effort by industry, and State, and Federal agencies to pool resources in an accelerated program of research on fishery chemicals.

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