US Army Corps
of Engineers
Waterways Experiment
Station

Zebra Mussel Research Technical Notes

November 1994

Registration Process Required by the USEPA for a New Pesticide

Background and purpose

Since the detrimental effects of zebra mussels were first recognized, many methods using previously existing chemicals, such as chlorine and bromine, have been proven highly successful in controlling this macrofouler. Frequently, facility managers, operators, and lay personnel inquire about the possibility of developing new pesticides for zebra mussel control. Before such compounds can be marketed, a permit has to be obtained from the U.S. Environmental Protection Agency (EPA).

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was enacted in 1972 by the EPA to monitor the registration and implementation of all chemicals intended for control of living organisms (Howe and others 1994). This law, in accordance with the Code of Federal Regulations (CFR) (title 40, Protection of the Environment, parts 150-189, dated 1985), regulates pesticide manufacture, use, disposal, and importation by requiring every proposed pesticide to be registered with the EPA before shipment, delivery, and sale in the United States (Worobec and Ordway 1989). Although FIFRA has been amended several times to speed up this process, pesticide registration remains lengthy and costly.

The EPA divides pesticide applications into three types: "new chemical," which concerns pesticides with active ingredients that are not already contained in previously registered pesticides; "new use," which concerns a different protocol of use for a previously registered pesticide; and "me-too," which concerns pesticides whose ingredients and uses are very similar to a currently registered pesticide (EPA 1989). The purpose of this technical note is to describe the registration process required by the EPA for an applicant to bring a new pesticide to the market. This assumes that the applicant has already determined that the chemical compound can be manufactured, developed, and applied without exorbitant cost, and that it is toxic to the target organism without undue hazardous effects to the environment or to nontarget organisms.

Additional information

This technical note was prepared by Ms. Fawn M. Burns, Rice University. Contact Dr. Andrew C. Miller, U.S. Army Engineer Waterways Experiment Station (WES), (601) 634-2141, for additional information. Dr. Ed Theriot, WES, (601) 634-2678, is Manager of the Zebra Mussel Research Program.

Prepared and published by the Zebra Mussel Research Program, U.S. Army Engineer Waterways Experiment Station, 3909 Halls Ferry Road, Vicksburg, MS 39180-6199.

Permit application process

Typically, the application process—from the commencement of research to pesticide registration and final label approval— requires between 5 and 10 years and between $7 and $15 million dollars. The majority of the time and funds is spent on research done by the registrant to determine the active ingredient's environmental effects beyond its pesticidal action and to demonstrate that the pesticide is effective in the manner claimed.

Most pesticide applicants spend approximately the first 2 years obtaining a patent for the pesticide and performing preliminary toxicology and efficacy testing (EPA 1984). The patent entitles the holder to temporary exclusive rights to the pesticide's active ingredient, which is crucial for the registrant's protection if the active ingredient is new to the market. The registrant's next step is to obtain an Experimental Use Permit (usually from the EPA, although some states issue them) so that major testing in the following 3 to 5 years can take place legally.

If a pesticide is to be used in an aquatic environment, FIFRA's label requirements also dictate that, in accordance with the Clean Water Act, the user must obtain a National Pollutant Discharge Elimination System (NPDES) permit from the appropriate EPA or state agency. This permit establishes that proper use of the pesticide does not violate the state's water quality-based effluent limits (Tsou 1992). Since the states are permitted to have requirements beyond those of the EPA, every state may have different requirements. Thus, a new pesticide might not receive approval in every state for several years; some pesticides never do, and therefore could be restricted to use in certain states. All testing, including safety studies mandated by the EPA, are conducted at the expense of the registrant.

The EPA's review and registration process fills the last 3 to 4 years of permit application. After submission of all the application materials described above, the EPA assigns the pesticide to a Product Manager, who handles that pesticide throughout the registration process and ensures that all necessary materials are submitted. Next, scientists at the EPA spend at least 2 years analyzing the data concerning environmental and health safety, judge the consistency of the log-keeping and laboratory methods with those dictated by FIFRA and the CFR, and make a judgment on whether the substance's properties are effective and not unduly hazardous. Additional or repetition studies may be requested at any stage in this process. If the pesticide is satisfactory, registration is approved, and a final label is written (EPA 1984).

The Good Laboratory Practices clause (40 CFR 160) entails great expense for the registrant. The testing facility and all records and specimens related to the pesticide study may be audited by an EPA member at random. This clause states that a "sufficient number of personnel for the timely and proper conduct of the study" must be employed, and the facility must have a quality assurance unit separate from the employees who conduct the actual research. The quality assurance unit is required to keep detailed records of protocols, inspect each phase of an experiment, and submit written accounts of each experiment to the study director. Reagents used must be labeled with their name, chemical abstract number, batch number, and expiration date; samples from each batch of reagents must be labeled and reserved for up to 5 years after the data have been submitted to the EPA (40 CFR 160). Each time an application is determined to be incomplete, EPA charges the registrant $1,200 for processing before it will return the application to the registrant for revision and resubmission (EPA 1989). FIFRA requires an additional fee of $425/pesticide/year to be paid to

the EPA after registration, not to exceed $20,000 for a single registrant each year.

The EPA guidelines for approving registration of a pesticide are vague. The statutes contain words such as "unreasonable risk" and "adverse effects" (40 CFR 158.75), both of which are difficult to define. A new chemical's value as a pesticide is based on reports by EPA economists, who compare the economic benefits of using the pesticide to the environmental risks. For zebra mussels the cost in damages that industry could expend without the pesticide would be weighed against the toxic effects of the pesticide on the environment (damage to humans, fish, birds, insects, groundwater, and air). If the benefits outweigh the risks, registration is approved. The EPA can also revise its data requirements at any time (40 CFR 158.85), making the application process risky.

The greatest cost and time commitment to the applicant ensues from the data requirements for registration. Residue chemistry testing is one of the most expensive areas of experimentation required, often extending into the millions of dollars. Also, negative effects of a pesticide often cannot be detected until that chemical is actually put into widespread use, after the entire registration process has taken place. If, after registration, a pesticide is found to have carcinogenic or oncogenic effects, to show developmental toxicity, risk of acute injury, or to have adverse effects on a nontarget organism, the EPA designates that pesticide to be under Special Review (40 CFR 154.7). The pesticide can be removed from the market if the EPA deems the action necessary after the Special Review process. In this case, more research and revision of prescribed usage must take place before the pesticide can be reregistered.

Under FIFRA, the EPA has the option to request additional studies during the registration process. In fact, a new trend is developing in the EPA to institute new required testing areas, such as immunotoxicity and behavioral toxicity, to reduce pesticide use and risk to children or to clarify a toxic effect of a problematic pesticide. The additional testing costs are borne by the applicant.

Information required by EPA

An application for pesticide registration with the EPA must contain:

- **Confidential Statement of Formula (EPA Form 8570-4).**
- **Five draft copies of the pesticide's proposed label.** The label must contain an ingredients statement, detailed usage instructions, and any applicable warnings. Proof that the NPDES permit, if required, has been obtained must also be submitted. A pesticide's label, in effect, becomes a legal document; violation of any of the above clauses can result in legal action against the consumer.
- **Three copies of all data pertinent to registration of the pesticide.** "Pertinent data" refers to results from extensive testing conducted by the applicant in regard to the pesticide. The nature of the tests is determined by the type of pesticide in question. For a general pesticide, data from testing in the areas of product chemical analysis, residue chemistry, product performance, toxicity, nontarget organisms, environmental fate, and expression data (40 CFR 158.120-160), in addition to data verifying that the labeling standards have been met, must all be submitted to the EPA.

  Toxicity testing alone includes acute oral toxicity, acute dermal toxicity, acute inhalation, primary eye irritation, primary dermal irritation, hypersensitivity studies, genotoxicity studies, immune response, 90-day

feeding, 90-day dermal, 90-day inhalation, mammalian mutagenicity and immune response testing, and oncogenicity.

The data submitted to the EPA must prove that the pesticide in question provides more benefits than risks when used in its designated protocol. Additional requirements are that the data must be submitted in the required format (40 CFR 158.32-34 and Procurement Request Notice 86-5) and that the registrant demonstrates that every experiment was conducted in careful accordance with the Good Laboratory Practices clause (40 CFR 160). If the EPA guidelines are not followed, the application will be rejected and returned for correction (EPA 1989).

Data may either be completely developed by the applicant, or may be a combination of the applicant's own data and data submitted to the EPA by previous applicants. If the latter method is chosen, the applicant must fulfill the data compensation requirements of FIFRA (section 3), which dictate that the previous applicant must agree in writing to supply the data to the new applicant, who must make a General Offer to Pay statement (40 CFR 152.86), and must pay the organization who gathered the additional data a negotiated amount.

Under section 23 of FIFRA, the states share responsibility with the EPA for pesticide regulation. Therefore, most states require specific registration of pesticides in addition to registration with the EPA. A pesticide can be designated for restricted use if it is judged as presenting a high risk to humans or to the environment (Worobec and Ordway 1989). Under these conditions, states often will require that a potential pesticide consumer be tested through written and/or performance methods to ascertain that the individual has "practical knowledge" (40 CFR 171.4) of the properties and proper usage of the pesticide.

Case history

The U.S. Fish and Wildlife Service (USFWS) sought to re-register and establish new tolerances for a lampricide (TFM) in 1970. After sending requested information to the EPA in 1978, USFWS waited until 1980 for a response. The EPA then indicated that further teratology and repeated residual studies were needed. Label changes were made between 1980 and 1983. Also, between 1983 and 1987, three individuals were assigned as Program Director for TFM, further delaying the process. Cost of the data-gathering process was estimated at $8 million, excluding developmental fees. Currently, TFM is still involved in the registration process; estimated completion time is 1994-1996 (Schnick 1990).

Hi-Tek Chemical Corporation began testing for their antifoulant coating, a copper-impregnated epoxy resin, in 1987. Since the coating is purely a repellent and, once applied, has not been shown to be toxic to living organisms, the EPA did not require as extensive testing as is usual for an aquatic or airborne pesticide. Hi-Tek found that hiring legal counsel as liaisons and having lobbyists in Washington, DC, proved invaluable to hastening registration since it increased their exposure to the EPA. Hi-Tek was able to begin the registration process in January 1989, when they hired a patent attorney. EPA consultants were also commissioned to hasten the process, at Hi-Tek's personal expense. Registration of EPCO-TEK 2000 was approved in August 1991.

Conclusion

The registration process for new pesticides is lengthy and expensive. The alternative, however, would be an excess of potentially dangerous substances, whose toxic effects would be discovered only by trial and error. EPA's goal is

to selectively permit chemicals into the market that improve our standard of living, without posing danger. Most chemical companies appear unwilling to expend the time and funding to develop a new pesticide for zebra mussels, especially since existing chemicals, as well as heat, antifoulant coatings, and oxidizing and nonoxidizing chemicals, are already available and effective.

References

Howe, P. H., Masters, E., Atteberry, R., and Redmon, P. 1994. "A Summary of Federal Regulations Related to Use of FIFRA-Registered Biocides and Region 5, USEPA, Use of These Biocides for Zebra Mussel Control," Technical Note ZMR-1-15, Zebra Mussel Research Program, U.S. Army Engineer Waterways Experiment Station, Vicksburg, MS.

Schnick, R. A. 1990. "A Chronology of Efforts to Reregister and Establish Tolerances for TFM: An Update," Special Report, National Fisheries Research Center, La Crosse, WI, pp 1-13.

Tsou, J. L. 1992. "Chemical Control Technology, Section 3," *Proceedings: Electric Utility Zebra Mussel Control Technology Conference,* Chicago, IL.

U.S. Environmental Protection Agency (EPA). 1984. "Registering Pesticides," *EPA Journal,* Vol 5, pp 25-26.

U.S. Environmental Protection Agency. 1989. "General Information on Applying for Registration of Pesticides in the United States," Section 2, Washington, DC.

Worobec, M. D., and Ordway, G. 1989. "Toxic Substances Controls Guide: Federal Regulation of Chemicals in the Environment," Bureau of National Affairs, Washington, DC.