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Recent regulatory requirements for pesticide registration and the status of Compound 1080 studies conducted to meet EPA requirements

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Abstract In the U.S., pesticides are registered by the Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). This act was amended in 1988 to require that each pesticide registered before 1984 be reregistered within a 9-year period. The reregistration process has increased data requirements and costs and has caused cancellation of many minor-use pesticides that do not generate sufficient profit to justify data generation costs.

In 1988, the U.S. Environmental Protection Agency (EPA) notified registrants of its intent to cancel the registration for the only Compound 1080 technical product (held by Tull Chemical Co.) and all Compound 1080 rodenticide use registrations. These notifications occurred because the registrants had not submitted required data to maintain the registrations. All rodenticide uses were subsequently cancelled in 1990. This resulted in the loss of a chemical critical to managing vertebrate pests. However, EPA allowed the Animal and Plant Health Inspection Service (APHIS) to maintain a technical Compound 1080 registration for use only in the APHIS Livestock Protection Collar (LPC). APHIS is currently providing data to reregister the Compound 1080 technical product. Prior to 1992, six product chemistry and three toxicology studies (acute dermal rabbit, eye irritation rabbit, and skin irritation rabbit) were submitted to the EPA, along with some non-target hazard studies. In a Data Call-In issued on September 30, 1992, EPA required only a minimal amount of additional data for the APHIS technical product. To date, APHIS has supplied 11 studies to the EPA under the 1992 Data Call-In: eight product chemistry studies, bluegill sunfish and rainbow trout toxicity studies, and an aquatic invertebrate toxicity study. Avian dietary toxicity studies on bobwhite quail and mallard duck are scheduled to be completed in April 1994.

Keywords Sodium monofluoroacetate; 1080; pesticide regulation

FEDERAL REGULATION OF VERTEBRATE PESTICIDES IN THE UNITED STATES

The history of pesticide regulation in the United States dates from the passage of the Federal Insecticide Act of 1910, which made it unlawful to sell adulterated products and protected purchasers of insecticides and fungicides from fraud (Fagerstone *et al.* 1990). Shortly thereafter, mammal control specialists recognized the need for a system to control pesticide use on wild animals. With passage of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1947, registration of rodenticides and rodent repellents was required and was administered by the U.S. Department of Agriculture (USDA). The scope of FIFRA was expanded in 1961 to include other mammals, birds, fishes, reptiles, amphibians, invertebrates, plants, and viruses (Ramey *et al.* 1992). In 1970 registration functions were transferred from USDA to the newly created Environmental Protection Agency (EPA). In 1972 FIFRA was amended by the Federal Environmental Pesticide Control Act (FEPCA), which increased EPA's authority to regulate the storage, sale, and use of pesticides (Fagerstone *et al.* 1990). It also established definitive criteria for pesticide registrations, including a lack of "unreasonable adverse effects" on human health or the environment. As a result of these changes, registration data requirements became much more comprehensive. In 1984, the EPA expanded the kinds of data that must be submitted to EPA to support a registration. The basic

data requirements for all pesticides registered in the U.S. fall into several broad categories: 1) product chemistry studies on the physical and chemical characteristics of the pesticide; 2) wildlife and aquatic organisms studies to determine toxicity to non-target species, such as avian toxicity and reproduction, and fish and aquatic invertebrate toxicity studies; 3) toxicology studies to determine possible effects of the pesticide on short or long-term human health; 4) non-target plant hazard evaluation studies to determine pesticide effects on seed germination and vegetative vigor; 5) environmental fate studies to monitor the movement, degradation, and/or metabolism of pesticides in soil, water, and air; and 6) residue chemistry studies to determine pesticide residues in food plants or animals for development of tolerances.

In 1988, the U.S. Congress amended FIFRA (FIFRA 88) to strengthen and accelerate EPA's reregistration program (Fagerstone *et al.* 1990). FIFRA 88 required that each product registered before 1984 be reregistered within a 9-year period. It also imposed a one-time registration fee and annual maintenance fees. FIFRA 88 specified a 5-phase reregistration process for approximately 600 active ingredients which are used to produce about 35,000 end-use products. Phase 1 of the reregistration process was a listing of the active ingredients of the pesticides on four lists in descending order of concern to EPA. In Phase 2, registrants submitted a notice of their intention to seek reregistration of their pesticides, and committed to supply missing and inadequate data for the technical products. During Phase 3, registrants submitted the data to EPA. During Phase 4 (which is currently in progress), EPA is reviewing data submissions from Phases 2 and 3, identifying outstanding data requirements and issuing Data Call-Ins for any required additional data. Phase 5 involves the final review of data for technical products, issuance of a Reregistration Eligibility Document and a Data Call-In for individual end-use products, and a regulatory action (such as reregistration or cancellation).

Increasing data requirements, and the associated costs of generating those data, have made it uneconomical for many private and public registrants to maintain any but the large-volume vertebrate pesticide uses. Most vertebrate pesticides are minor-use pesticides with low-volume use compared with insecticides, fungicides, and herbicides. Because of FIFRA 88, many vertebrate pesticide uses of importance to the agricultural community, the public, and governmental animal damage control and public health personnel have been cancelled or have had their uses restricted. Manufacturers have dropped low volume pesticides such as Compound 1080 because use and sales cannot economically justify the cost of registration fees, annual maintenance fees, and data generation. Compound 1080 was especially vulnerable to cancellation because state and federal agencies were reluctant to deal with the unfavorable public opinion which this chemical evokes.

Other recent regulations impacting U.S. pesticide registrations

In addition to FIFRA 88, two other recent regulations have impacted vertebrate pesticide availability by increasing the cost of research (Fagerstone *et al.* 1990). New data generated because of FIFRA 88 must conform to EPA's Good Laboratory Practice Standards (GLPs) and animal studies must follow guidelines of the Animal Welfare Act. The GLPs were issued by EPA in 1983 to ensure that testing for Human Health Hazards was conducted properly and that all raw data were retained. GLP standards require that: 1) studies are defined by an approved protocol; 2) qualified personnel are in charge of the study; 3) the study is conducted according to written Standard Operating Procedures; 4) equipment is properly calibrated and maintained; 5) data are properly gathered and recorded; 6) raw data are saved for future review or EPA audit; and 7) a Quality Assurance Unit is established at each laboratory to assure that the standards are met. As of October 1989, all studies used to support pesticide registrations were required to meet GLPs.

The Animal Welfare Act was enacted in December 1985, and provides regulations and standards for humane handling, housing, care, treatment, and transportation of animals. The Act requires that animal facilities have an attending veterinarian, and that a committee be established to review every protocol that deals with the use of animals. The Act also sets standards for housing and care of animals, and provides for periodic inspection of facilities holding animals.

Impact on number of pesticide registrations

Registration cancellations have occurred at a high rate since 1988, as registrants were initially required to pay registration and maintenance fees, and then

were required to submit data. Of the 44,000 pesticide products on the market in 1988 (containing more than 600 active ingredients) fewer than 20,000 are now available, and the number of active ingredients has dropped to 407. Chemical manufacturers are voluntarily cancelling minor use pesticides because sales from these uses do not pay for the high costs of generating the data required by EPA.

HISTORY OF 1080 USE IN THE UNITED STATES

Rodenticide and predacide baits

Compound 1080 (sodium monofluoroacetate) was first prepared by Swartz in 1896 (Pattison 1959), but it was not used as a vertebrate pesticide until World War II, when shortages of strychnine and red squill in the United States and England necessitated the development of other chemicals. Research on Compound 1080 for use as a predacide in baits was carried out by the Denver Wildlife Research Center (DWRC) in the late 1940's and 1950's (Connolly 1980) and it was used to control coyotes (*Canis latrans*) for about 25 years. All predacide uses were halted in February 1972, when President Nixon issued an Executive Order prohibiting use of secondary poisons (including strychnine and Compound 1080) on federal lands or by federal agencies. Since then, Compound 1080 has not been used for predator control except for its use in the Livestock Protection Collar (LPC). In the late 1960's about 98 percent of the Compound 1080 sold in the United States was used against rodents, so the 1972 ban on predator control had little effect on the total amount of Compound 1080 used (Connolly 1980). By 1975 all U.S. Fish and Wildlife Service rodenticide registrations for Compound 1080 had been voluntarily cancelled and the majority of Compound 1080 was used in a few states (primarily California). In 1984, the EPA issued a Data Call-In for Compound 1080. When adequate data were not submitted, the EPA notified registrants in 1988 of its intent to suspend or cancel the registration for the only Compound 1080 technical product (held by Tull Chemical Co.) and all the Compound 1080 registrations for rodenticide uses. All rodenticide uses were cancelled in 1990.

Consideration is currently being given to attempting to again register a Compound 1080 technical for rodenticide use in the U.S. However, costs may be prohibitive. Use of Compound 1080 technical in rodenticide baits is classified as a terrestrial non-food use—meaning pesticides are placed outdoors in non-agricultural areas, in underground burrows, or on rangeland on bare ground around burrows (broadcast baiting on rangeland is considered to be a food use because of the potential for consumption by livestock). For the terrestrial non-food use pattern, the minimum estimated cost would be over $720,000 to conduct three product chemistry, nine wildlife and aquatic toxicity, four toxicology, and five environmental fate studies to supplement data gathered to support the existing Compound 1080 technical registration for LPC use only. In addition, the minimum estimated cost for registration of an end-use product would be about $100,000 for 13 product chemistry, one toxicology, and six wildlife and aquatic toxicity studies. Costs would be less for each additional end-use product using similar formulations. EPA would also require efficacy studies at a cost of about $100,000 for each species. If Compound 1080 is to be reregistered as a rodenticide in the U.S., then producers, sellers, and user groups will have to look at innovative funding mechanisms to help the technical registrant conduct required studies.

Livestock protection collar

The Livestock Protection Collar (LPC) is a collar containing Compound 1080 that fits around the neck and throat of a lamb or kid goat. Because coyotes most commonly kill sheep or goats by biting their throats, the collar is designed to rupture where bitten, thereby releasing a solution containing Compound 1080 and killing the offending coyote (Connolly 1993). The LPC is effective in removing coyotes that have avoided other types of control methods. Its greatest advantage is its selectivity, as only the individual coyote that attacks sheep is killed. The LPC was invented by Roy McBride (Ranchers Supply, Alpine, Texas) in the early 1970's and patented in his name by the U. S. Government in 1974. Intensive research by the DWRC and others led to EPA registration in 1985.

APHIS now holds the only technical registration (EPA Reg. No. 56228–26) for Compound 1080 and is providing all of the required data to reregister Compound 1080 technical for use only in the LPC. The APHIS technical registration does not cover rodenticide uses. APHIS also holds a registration for the LPC (EPA Reg. No. 56228–22), including a small collar for use on lambs or kid goats

and a larger collar designed to be placed on animals weighing over 50 pounds. The LPC is also currently registered for use by state-certified applicators in Texas, Montana, South Dakota, Wyoming, and New Mexico.

APHIS has received waivers for many data requirements for the Compound 1080 technical that is used only in the LPC because: 1) Compound 1080 qualifies as a low volume minor use pesticide (with less than one pound sold for this use each year), and 2) use of Compound 1080 in a collar around the neck of a sheep provides only negligible exposure of 1080 to non-target wildlife or the environment.

Prior to 1992, the DWRC submitted six product chemistry and three toxicology studies, plus some non-target hazard data, to the EPA. In a Data Call-In. issued on September 30, 1992, EPA requested additional data for the LPC technical product. To date, APHIS has supplied eight product chemistry studies, two fish toxicity studies (bluegill sunfish (*Lepomis macrochirus*) and rainbow trout (Oncorhynchus mykiss)), and one aquatic invertebrate toxicity (*Daphnia magna*) study to the EPA under the 1992 Data Call In. Two avian dietary toxicity studies with bobwhite quail (*Colinus virginianus*) and mallard duck (*Anas platyrhynchos*) are scheduled to be completed in April 1994.

REQUIRED STUDIES FOR THE LIVESTOCK PROTECTION COLLAR

The following studies have been submitted to the EPA or are being conducted under EPA guideline numbers (GDLN) to fulfill the data requirements of reregistration of Compound 1080 technical product for use in the Livestock Protection Collar. Fifteen product chemistry studies have been conducted (EPA = Submitted and Accepted by EPA):

GDLN No.	Study	Status
61–1	Chemical Identification	EPA
61–2(a)	Manufacturing Process	EPA
61–2(b)	Impurities Analysis	EPA
62–1	Preliminary Analysis	EPA
62–2	Certification of Limits	EPA
62–3	Analytical Method	EPA
63–2	Color	Submitted
63–3	Physical State	EPA
63–4	Odor	Submitted
63–7	Density	EPA
63–8	Solubility	Study In Progress
63–10	Dissociation Constant	EPA
63–12	pH	EPA
63–13	Stability	Submitted
63–17	Storage Stability	EPA

Avian toxicity studies

Two avian dietary toxicity studies are being conducted and will be completed during 1994. These are GDLN 71–2(a) Acute Dietary Toxicity—Bobwhite Quail, and GDLN 71–2(b) Acute Dietary Toxicity—Mallard Duck.

Aquatic toxicity studies

During September 1993, APHIS submitted three aquatic toxicity tests to the EPA. The first was GDLN 72–1, Acute Toxicity Test with Bluegill Sunfish (*Lepomis macrochirus*), which estimated the acute toxicity of 1080 to bluegill sunfish under static renewal test conditions (Collins *et al.* unpubl. data). Following the termination of the test at 96 h, no mortality or sublethal effects were observed at any concentration tested; therefore, the no-observed-effect concentration (NOEC) was determined to be 970 mg L^{-1}, the highest concentration tested. Based on the results of this study and criteria established by the U.S. EPA (1985a), Compound 1080 would be classified as practically non-toxic to bluegill sunfish (Table 1).

The second test was GDLN 72–1, Acute Toxicity Test with Rainbow Trout (*Oncorhynchus mykiss*), which used the same test conditions as the bluegill sunfish studies (Collins *et al.* unpubl. data). Following the termination of the test at 96 h, mortality ranging from 50 to 90% was recorded in the 4 treatment levels ranging from 39 to 170 mg l^{-1}. In addition, 10% mortality was observed at the 23 mg l^{-1} treatment level. Sublethal effects were

Table 1 Descriptive classification used by the EPA to compare LC_{50} (EC_{50}) toxicity among chemicals.

LC_{50} mg l^{-1}	Description
< 0.1	very highly toxic
0.1 – 1	highly toxic
> 1 10	moderately toxic
> 10 100	slightly toxic
>100	practically non-toxic

observed among surviving fish exposed to levels over 23 mg l^{-1}. No mortality or sublethal effects were observed among rainbow trout exposed to the 13 mg l^{-1} level. The 96 h LC_{50} value for rainbow trout was calculated to be 54 mg l^{-1} with 95% confidence intervals of 39–74 mg l^{-1}. The NOEC was 13 mg l^{-1}, which the U.S. EPA (1985a) classifies as slightly toxic to rainbow trout (Table 1).

The third aquatic toxicity test was GDLN 72–2, Acute Toxicity Test with *Daphnia magna*, which estimated the acute toxicity (EC_{50}) of Compound 1080 under static renewal test conditions (Collins *et al.* unpubl. data). The EC_{50} is defined as the concentration in dilution water which causes immobilization of 50% of the exposed daphnids. Following the termination of the test at 48 h, 70 to 100% immobilization was observed among daphnids exposed to levels of 350 to 980 mg l^{-1}, respectively. Immobilization of 5% was observed among daphnids exposed to 220 mg l^{-1}. Sublethal effects were observed among all of the mobile daphnids exposed to 220 to 590 mg l^{-1} but were not observed among those exposed to 130 mg l^{-1}. The 48 h EC_{50} value for daphnids exposed to Compound 1080 was calculated to be 350 mg l^{-1} and the NOEC was determined to be 130 mg l^{-1}. The results of this test indicate that Compound 1080 is practically non-toxic to *Daphnia magna* (U.S. EPA 1985b; Table 1).

Toxicology

APHIS has submitted three rabbit toxicology studies to the EPA (Savarie & Cerven, unpublished data). The first study was GDLN 81–2, Acute Dermal Toxicity—Rabbit. In this test, five male and five female albino rabbits for each of four dose levels were treated dermally with a 1080 paste. The estimated LD_{50} was 324 mg kg^{-1} for females and 277 mg kg^{-1} for males. Based on these data, Compound 1080 was classified as a Category II dermal toxicant (Table 2). The second test was GDLN 81–4, Primary Eye Irritation—Rabbit. In this test six albino rabbits were treated with a 1% solution of Compound 1080, which was placed into the conjunctival sac of the eye; ocular responses were recorded for up to 3 days. Compound 1080 caused no corneal opacity, or iritis, and only slight conjunctival irritation. Compound 1080 was classified as a Category III ocular irritant (Table 2). The last test conducted was GDLN 81–5, Primary Dermal Irritation—Rabbit. Six albino rabbits were treated dermally with 1% Compound 1080 by keeping the chemical in contact with the skin for 4 h. Compound 1080 did not cause erythema and edema was absent to slight at 5 h but absent thereafter. Compound 1080 was classified as a Category IV dermal irritant (Table 2).

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Table 2 EPA toxicity category chart for human health hazard studies. † Adopted from U.S. Code of Federal Regulations 40 CFR 156.10 (h)(1)(i), July 1, 1991. *Adopted from PR NOTICE 81–3, Notice to Manufacturers, Formulators, Distributors and Registrants fo Pesticides — Label Improvement Program: Change in Test Methods for and Categorization of Eye Irritation, dated 9/29/81.

	Toxicity Categories			
Hazard Indicators	I	II	III	IV
Dermal LD_{50} (mg kg^{-1})†	200	> 200 2,000	> 2,000 20,000	> 20,000
Eye effects*	Corrosive (irreversible destruction of ocular tissues) or corneal involvement or irritation persisting for more than 21 days	Corneal involvement or irritation clearing in 8 – 21 days	Corneal involvement or irritation clearing in 7 days or less	Minimal effects clearing in less than 24 hours
Skin Effects†	Corrosive	Severe irritation at 72 hours	Moderate irritation at 72 hours	Mild or slight irritation at 72 hours

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