Integrated Management Techniques to Control Nonnative Fishes

Completion Report
Interagency Agreement Number: 01-AA-32-0040

Prepared for

Bureau of Reclamation
P.O. Box 81169, Phoenix, Arizona 85069-1169

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December 2003

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Abstract

Many species of native fish from the southwestern United States, including those in the Gila River basin in Arizona and New Mexico, are critically imperiled in part because of the introduction and establishment of nonnative fishes. Effective methods for eradication and control of nonnative fishes are needed to rehabilitate the imperiled native fish fauna of the Gila River basin. The objective of this report is to assess the potential of applying techniques of integrated pest management to protect imperiled native fishes in the southwestern United States from invasive nonnative species. To accomplish this, reviews of pertinent literature were conducted in selected topic areas and the information presented in a series of chapters to document findings. Subject areas of the review included (1) life-history strategies for both native and nonnative species in those waters; (2) evaluation, identification, and characteristics of successful integrated pest management programs; (3) identification of potential and existing chemicals and appropriate chemical formulations for use as general and selective piscicides; and (4) procedures and costs associated with the discovery and development of new and perhaps taxon-specific piscicides. Characteristics of native fishes of concern were compared with those of nonnative fishes, and the geographic ranges of native and nonnative fishes were mapped to identify potentially vulnerable conditions around which control strategies could be developed. The concept of chemical receptors and receptor responses are presented to help explain the basis of selective toxicity. A total of 45 chemicals were identified that have either been used as piscicides, or are currently in various stages of development. A rating system was developed that evaluates the usefulness of these chemicals in resolving problems caused by nonnative fishes. Only five of the chemicals (antimycin, rotenone, TFM, Bayluscide®, and Squoxin) achieved ratings of 75 or greater out of a possible score of 100. Chemical reclamations have not always been successful as indicated by reviews of hundreds of fish control projects with reported successes ranging from 43% to 82%. It is unlikely that the present arsenal of approved selective piscicides would be effective for controlling nonnative fishes in the southwestern United States because the fish communities are different from most areas where selective piscicides are being used, and the currently registered taxon selective piscicides target sea lampreys. A comprehensive list of formulations and associated delivery systems for applying registered piscicides are presented. The development of new chemical tools for selectively managing fish populations may be facilitated by the knowledge of the mode of action of candidate piscicides and their structure-toxicity relationships. An evaluation of the costs and benefits of chemical treatments, as well as the cost associated with the development and registration of new piscicides, are provided. Reclamation of habitats that are critically imperiled by invasive fishes may need to be implemented using general piscicides such as antimycin or rotenone. This would require that important extant native species be temporarily moved to refugia until after the treatments. In less critical situations, efforts could be directed toward development of integrated pest management techniques that include development and use of barriers, water-level manipulations, targeted overharvest, stocking of predators, sterilants, toxic baits, selective piscicides, attractants and repellants, immuno-contraceptive agents, viruses, chromosomal manipulations, gynogenesis, and transgenics.

Key words: Arizona, control of nuisance fishes, Gila River basin, integrated pest management, nonnative fishes, reclamation, selective removal, southwestern United States, taxon-selective piscicides

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Chapter 1. Introduction

by Cynthia S. Kolar

The biodiversity of native fishes in Arizona, with approximately 30 native species recorded since the late 1800s (Minckley 1973, Rinne 1995), is low compared with the specious freshwater fish faunas of the eastern United States. High rates of endemism characterize fishes from the southwestern United States; specialization of form is the rule rather than the exception (Rinne 1995). In the Gila River basin, which drains approximately 212,380 km^2 in Arizona and New Mexico, 5 of 17 native fishes are the only species in their genus (Miller 1961, Rinne 1995). Fishes native to the southwestern United States typically are adapted to tolerate waters of high temperature or salinity. They are also habitat specialists in areas such as thermal springs or highly erosive streams, but have evolved generalizations that promote resistance to extinction (Minckley and Meffe 1987).

While habitat specialization has enabled these fishes to persist in habitats few other species can withstand, it has also left them vulnerable to habitat alterations and invasive species. As the human population has grown throughout the region and demand for water has intensified, aquatic ecosystems have been greatly altered. Numerous dams and intensive livestock grazing practices have changed water temperatures and flow regimes, usually reducing habitat quality for native fishes (Rinne and Minckley 1991). Fish introductions, mostly for sport and food, but also from aquaculture, aquarium releases, additional forage, and for biological control have also been common in the southwestern United States (Rinne 1995). The number of fish species established in Arizona has almost tripled since the beginning of the 20th century as a result of the introduction of nonnative fishes (Rinne 1991). Many of these introduced fishes are better adapted to the highly altered systems now found in the southwestern United States than are native species (Rinne and Minckley 1991). As a result, native fishes of the southwestern United States are becoming increasingly imperiled.

Of the approximately 20 fishes native to the Gila River basin, the largest watershed in Arizona, around 70% are federally listed as endangered or threatened (Rinne 2003), and one is extinct. The plight of native fishes in this basin is typical of most basins in the southwestern United States. The inherent rarity of fishes native to the southwestern United States is exacerbated by factors such as habitat alteration and the introduction of nonnative fishes (Minckley and Meffe 1987). Along with habitat alteration and destruction, competition with and predation by nonnative fishes have been identified as the driving forces for the imperilment of many of the native fishes of concern in the Gila River basin (Table 1-1). Twelve of these native species and twelve nonnative species have been identified as those of most concern in discussions with Bureau of Reclamation personnel and literature sources (Table 1-2). In some instances, self-sustaining populations of native fishes appear to be unable to persist in habitats where nonnative fishes have become established (Marsh and Pacey, in press). For example, in areas where the introduced red shiner (scientific names of fishes used in this report are found in Appendix A) are

Table 1-1. Population status and summary of primary threats for native fishes of concern in the Gila River basin. Scientific names are given in Appendix A. SOC = U.S. Fish and Wildlife Species of Concern.

Common name	Status	Primary threats
Desert sucker	SOC (1)	Stream flow depletion, diversion, and introduction of nonnative species; competition by red shiner (1).
Sonora sucker	SOC (1)	Stream flow depletion, diversion, and introduction of nonnative species (1); predation by nonnative species, especially flathead catfish (2).
Spikedace	Threatened 1986 (2)	Stream flow depletion, diversion, habitat alterations, competition and predation by nonnative species, especially crayfish and red shiner (2). As of 1997, Arizona populations limited to Aravaipa Creek and upper Verde River (1).
Razorback sucker	Endangered 1991 (2)	Altered flow hydrology, cool tailwater discharge from reservoirs, diversion, predation by and competition with nonnatives. Wild populations extirpated (3). Habitat loss (e.g., flooded bottomlands), degradation, and fragmentation. Predation by nonnative red shiner, ictalurids, and centrarchids (1).
Loach minnow	Threatened 1986 (2)	Dewatering of stream reaches, impoundment, livestock grazing, habitat alteration, and introduction of nonnative fish, predation by piscivorous species, such as flathead and channel catfishes, bullheads, and red shiner (2). Sedimentation and embedding of riffle habitats, diversion, and channelization. Competition by introduced nonnative species, such as *Micropterus* spp. (1)
Longfin dace	SOC (1)	Stream flow depletion, diversion, invasion of nonnative fishes. Considered to be the most successful and highly adaptable native cyprinid in the desert Southwest (1).
Gila chub	SOC (1), proposed as endangered (3)	Stream flow depletion, diversion, competition and predation by introduced nonnatives, especially crayfish and largemouth bass. Extirpated from New Mexico (2). Dewatering of spring habitats by arroyo cutting. Present in less than 20 streams in central and southern Arizona (1).
Desert pupfish	Endangered 1986 (2)	Spring habitat alterations, drought, predation by and competition with nonnative fishes. No natural populations remain in Arizona (2). Reintroduced in 1983 into four areas (1).
Speckled dace	SOC (1)	Introduction of nonnative predatory fishes. Widespread and abundant and not in danger of extinction (2).
Gila topminnow	Endangered 1967 (1)	Spring habitat development, aquifer pumping, habitat destruction, drought. Predation by and competition with nonnative fishes (2). Predation by introduced mosquitofish (1).
Roundtail chub (4)	SOC (1), petitioned for federally endangered (3)	Aquifer pumping, stream diversion, reduction in stream flow. Predation by and competition with nonnative fishes. Habitat destruction and parasites (1). Several mainstem river populations extirpated (3)

(1) Biota Information System of New Mexico (2000) (2) Arizona Game and Fish (2001) (3) Desert Fishes Team (2003) (4) Headwater chub *Gila nigra* is a recently described species that was split from the roundtail chub

Table 1-2. Native and nonnative fishes considered in this report to be species of concern in the Gila River basin.

Order	Family	Common name	Scientific name
		Native species	
Cypriniformes	Cyprinidae	Loach minnow	*Tiaroga cobitis*
		Spikedace	*Meda fulgida*
		Roundtail chub	*Gila robusta*
		Headwater chub	*G. nigra*
		Gila chub	*G. intermedia*
		Longfin dace	*Agosia chrysogaster*
		Speckled dace	*Rhinichthys osculus*
	Catostomidae	Sonora sucker	*Catostomus insignis*
		Desert sucker	*C. clarki*
		Razorback sucker	*Xyrauchen texanus*
Cyprinodontiformes	Poeciliidae	Gila topminnow	*Poeciliopsis occidentalis*
	Cyprinodontidae	Desert pupfish	*Cyprinodon macularius*
		Nonnative species	
Cypriniformes	Cyprinidae	Red shiner	*Cyprinella lutrensis*
		Common carp	*Cyprinus carpio*
Siluriformes	Ictaluridae	Channel catfish	*Ictalurus punctatus*
		Flathead catfish	*Pylodictis olivaris*
		Black bullhead	*Ameiurus melas*
		Yellow bullhead	*A. natalis*
Perciformes	Centrarchidae	Smallmouth bass	*Micropterus dolomieu*
		Largemouth bass	*M. salmoides*
		Green sunfish	*Lepomis cyanellus*
		Bluegill	*L. macrochirus*
		Redear sunfish	*L. microlophus*
Cyprinodontiformes	Poeciliidae	Mosquitofish	*Gambusia affinis*

found in Arizona, two native federally threatened species—spikedace and loach minnow—are absent (Minckley 1973). Spikedace and loach minnow have also been replaced by introduced fishes such as channel catfish and flathead catfish in some Arizona rivers (Rinne 1995).

To be successful, Rinne (1995) suggests that conservation of the native fishes in the southwestern United States requires that biologists be innovative and vigilant and should include research on the interactions of native and nonnative fishes. Restrictions on the importation of nonnative fishes, incorporation of a value system for native fishes, and a focus on the conservation and restoration of habitats for native species would also be required (Rinne 1995). Where historically inhabited waters are no longer suitable for native species because they are occupied by nonnative fishes, successful conservation of native fishes may rely on the removal or substantial reduction of nonnative fishes.

Effective treatments for the eradication and control of nonnative fishes include chemical renovation of stream reaches (usually in concert with installation of physical fish barriers), followed by the stocking of desired species (Rinne and Turner 1991), or application of species-specific piscicides in rare situations. Application of a species-specific piscicide is an intuitively appealing approach for controlling nonnative fishes, but has not been practiced in the southwestern United States because such piscicides are not available for the nonnative species of concern in the region. Chemical renovation is expensive, logistically difficult, usually more effective in smaller headwater areas, and usually requires retreatment for success. Other strategies (e.g., selective harvest, regulatory control) are generally not effective in controlling fishes. Thus, effective management of nuisance nonnative fishes in the southwestern United States, as well as in other ecosystems, probably will need to integrate various methods of control into one management program. For example, the use of piscicides combined with other innovative approaches—such as the use of sterilants, attractants or repellants, or reproductive inhibitors—that are used in an integrated manner to manage against nonnative fishes may improve the probability of successful renovation of streams and rivers in the southwestern United States. In addition, natural events such as flooding or fires that remove nonnative fishes could be exploited. The chapters in this report address the nonnative fish ecology, distributions, and their impacts on native fishes in the southwestern United States and provide background information on how similar situations have been and are being handled in other locations. They also provide methods and insights for developing new management tools and suggestions for programs involving integrated pest management.

Kolar et al. (Chapter 2) describe the biological and ecological characteristics of fishes found in the Gila River basin. Characteristics of each life stage, habitat preferences, and physicochemical tolerances of native fishes of concern are compared with those of nonnative fishes to identify potential conditions around which control strategies might be developed.

Gingerich and Stehly (Chapter 3) discuss piscicides with an introduction to the science of toxicology and the scientific basis for selective toxicity. This is followed by a brief overview of what makes toxicants selective to particular species including species differences in biochemistry and differences among species in their ability to process toxicants. The concept of using physiologically based pharmacokinetic models is discussed in the context of developing and screening selective fish toxicants.

Dawson (Chapter 4) provides a comprehensive literature review to identify currently registered and potential, but unregistered, general and taxon-specific piscicides. Each chemical is rated on its potential for use as a piscicide based on selectivity for target species, ease of application, safety to humans, rate of degradation to nontoxic materials, cost, and its persistence in animals, plants, or the physical environment.

Dawson (Chapter 5) reviews some of the past successes and failures of using piscicides to remove undesirable fishes. The review provides some insight concerning the potential for successful piscicide treatments and ways to avoid certain problems. Based on the high percentage of failed treatments, there is an apparent need for improving piscicides, formulations, and methods of application. Also, suggestions are provided for using piscicides in conjunction with a variety of integrated pest management techniques.

Boogaard (Chapter 6) highlights current formulations of piscicides and the techniques and equipment used to deliver them to the aquatic environment. He lists active and inert ingredients and manufacturers of each formulation of piscicide currently registered by the U.S. Environmental Protection Agency (EPA). Factors to consider when choosing a delivery system for a chemical treatment are provided.

Gingerich (Chapter 7) identifies newly discovered chemicals that may prove useful as candidates for future development as piscicides. He describes identified chemical inhibitors of energy production and proposes through structure-activity relationships how these classes of compounds may provide candidates for new piscicides in the future. Suggestions are provided for development of specific combinations of currently registered piscicides to provide selective toxicity between target and nontarget fishes of concern.

Hubert (Chapter 8) presents the process of piscicide development from start to finish. This includes screening or developing chemicals, testing and refining procedures, identifying possible development laboratories, describing environmental regulatory constraints and procedures, and estimating time and cost for research, development, and production.

Hubert and Dawson (Chapter 9) discuss the development of a focused integrated pest management strategy. They describe the types and forms of integrated pest management systems needed to achieve pest control goals. Integrated pest management systems include chemical, biological, and physical controls. Examples are provided of integrated pest management systems that are currently in use and in various stages of development.

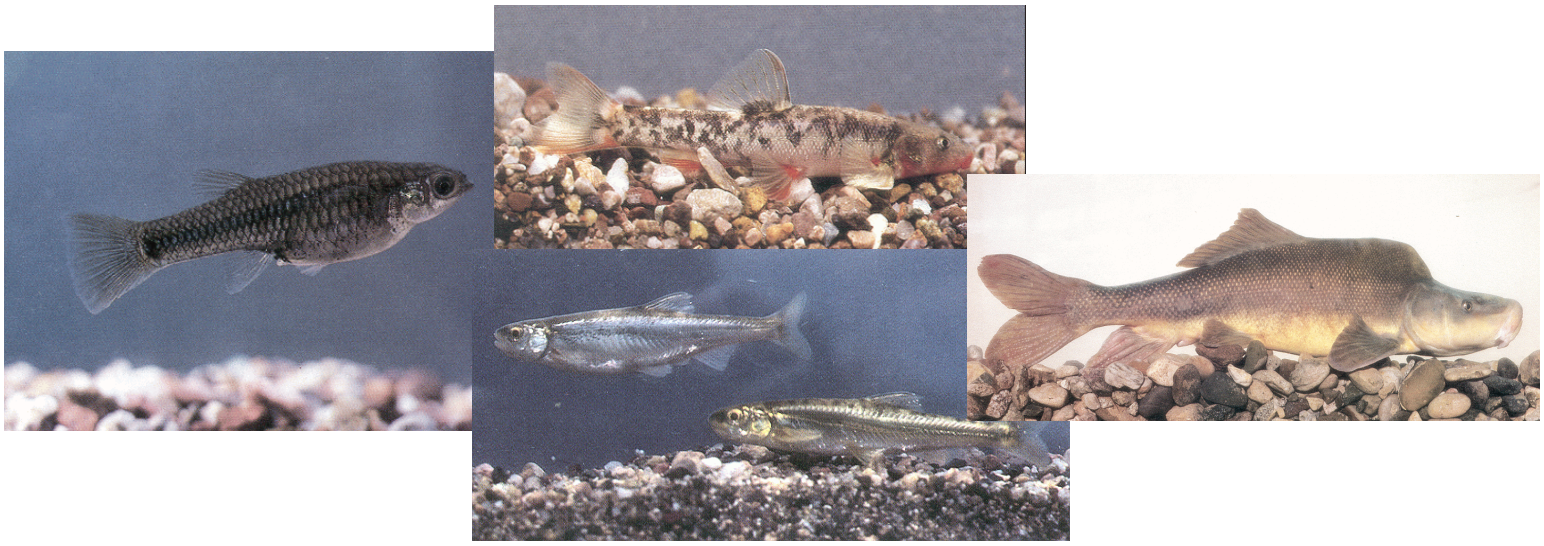
Hubert (Chapter 10) analyzes the costs and benefits associated with development of a pest control program. Included is an assessment of the costs and time involved in registering a piscicide with the EPA. An analysis of factors contributing to the cost of piscicide treatments is balanced against the benefits to recreational and commercial fishing and the ecosystem.

Kolar et al. (Chapter 11) discuss a case study of a successful fish control program. This includes the life history of the target organism, selection and development of piscicides, formulations, and application methods, and development of an integrated pest management program.

Dawson (Chapter 12) evaluates the feasibility of developing taxon-specific piscicides for management of nonnative fishes in the southwestern United States. Difficulties associated with management of selected taxa are discussed along with suggestions for using currently registered toxicants for urgently needed reclamations while developing new integrated management tools and incorporating them into future management programs.

Dawson and Kolar (Chapter 13) describe integrated pest management scenarios that generally involve use of chemicals in combination with other management techniques. Comparative toxicities of registered piscicides to native and nonnative fishes of concern are provided. Also provided are suggested treatment concentrations and costs for each piscicide.

Dawson (Chapter 14) provides a summary of topics that are included in this report on integrated management techniques to control nonnative fishes. Recommendations as to whether or not to proceed with development of piscicides or an integrated management program for nonnative fishes in the southwestern United States are discussed.



Chapter 2. Distribution and Ecological Characteristics of Native and Nonnative Fishes of Concern in the Gila River Basin

by Cynthia S. Kolar, Michelle R. Bartsch, John E. Kalas, and Brent C. Knights

Evidence shows that the imperilment of native fishes of concern in the Gila River basin results, in large part, from direct and indirect negative interactions with nonnative fishes (Table 1-1). Successful conservation of these fishes depends on (1) habitat protection and restoration, (2) greater knowledge of the interactions between native and nonnative fishes (Rinne 1991, Rinne 2003), (3) preventing the further introduction and spread of nonnative fishes, and (4) the control and removal of nonnative fishes from some waters.

Before developing control strategies for nonnative fishes in the Gila River basin, it is important to closely examine their biology and distribution. A thorough understanding of the biology and distribution of nonnative species may identify life stages, habitats, and geographic locations where control could be most effective. Likewise, a thorough understanding of the biology and distribution of native species of concern would allow for the development of control strategies that maximizes the probability of reducing or removing nonnative species while minimizing impacts to native species of concern.

Information on the life-history characteristics and physicochemical tolerances of these species were collected and summarized. Life-history information on native and nonnative fishes was compiled from selected literature and summarized in a referenced format (Appendix B). Species-specific information on habitat preferences, biology, and physicochemical tolerances are presented by life stage. Data on the history of invasion, threatened and endangered status, and the degree to which the species is used by humans were also collected for each species (see Table 2-1 for description of characteristics). Life-history data were collected from a variety of sources, including pertinent primary and gray literature, Web sites, and expert opinion. See Pacey and Marsh (1998) for life-history information of nonnative fishes of the Lower Colorado River, which also includes several species in the Gila River basin. Life-history characteristics and tolerances of native fishes of concern were statistically compared with those of nonnative fishes of concern by one-factor analysis of variance. Data used in these analyses can be found in Tables B-13 and B-14 of Appendix B.

Table 2-1. Explanation of the species characteristics collected for each native and nonnative fish of concern in Arizona and results of one-way analysis of variances comparing these characteristics. Data used to conduct analyses found in Tables B-13 and B-14 of Appendix B. Bold indicates variables for which substantial amounts of data were lacking. N = native species; NN = nonnative species; * = $P \leq 0.05$; ** = $P \leq 0.01$.

Characteristics	Variable	How species characteristic was evaluated (units)	*P*	Direction
Human use	Categorical	Human uses of fishes were ranked by economic benefit and ranks of all uses for each species were summed [Kolar and Lodge 2002].	**	N<NN
Introduction history	Yes/no	Whether the species has a history of introduction [Froese and Pauly 2002].	**	N<NN
Past invasiveness	Yes/no	Whether the species has a history of spreading greatly beyond the site of introduction [Froese and Pauly 2002].	**	N<NN
Family	Rank	Ranking of fish families from the most ancestral to the most derived [Moyle and Cech, Jr. 2000].	*	N<NN
Habitat type	Categorical	Whether the species lives in lotic or lotic and lentic environments.	**	N<NN
Mature length	Continuous	Average length (cm) at sexual maturity.	0.36	
Mature age	Continuous	Average age (year) at sexual maturity.	0.12	
Longevity	Continuous	Average life span (year).	0.87	
Diet items	Categorical	Diet breadth and diversity of foraging habitats [Kolar and Lodge 2002].	0.88	
High temperature	Continuous	Maximum lethal temperature (ºC) threshold.	*	N<NN
Egg diameter	**Continuous**	**Average diameter (mm) of mature ova.**	**0.26**	
Incubation	**Continuous**	**Average length of time (days) from spawning of eggs until hatching.**	**0.23**	
Fecundity	**Continuous**	**Average number of eggs produced by a mature female per year.**	*	**N<NN**
Larval length	**Continuous**	**Average length (mm) of newly hatched larva.**	**0.76**	
Spawning seasons	Rank	Number of seasons (1-4) during which the species spawns in Arizona.	**	N>NN
Parental care	Categorical	Ranked by amount of parental care provided to young [Kolar and Lodge 2002].	*	N<NN

The analyses highlighted the important differences between the native and nonnative fishes of concern in Arizona in terms of developing control strategies for nonnative fishes (see Table 2-1): most of the nonnative fishes of concern were purposefully stocked because they had a successful history of being stocked elsewhere (history of introduction; $F_{1,20} = 45.00$, $P < 0.0001$) and were perceived as being useful either for sport, forage, or biological control (human use, $F_{1,20} = 42.61$, $P < 0.0001$). Nonnative fishes of concern in the Gila River basin also have a history of being invasive elsewhere whereas native fishes do not (past invasiveness; $F_{1,20} = 12.00$, $P = 0.03$). In addition, the nonnative species selected for stocking (i.e., catfishes and sunfishes), tended to be from more phylogenetically advanced families than native species (family; $F_{1,20} = 5.74$, $P = 0.03$). When compared with nonnative species, native species were more confined to flowing lotic habitats (habitat type; $F_{1,20} = 26.67$, $P < 0.0001$), had lower maximum temperature thresholds (high temperature; $F_{1,19} = 5.42$, $P = 0.03$), lower fecundity (fecundity; $F_{1,20} = 4.5$, $P = 0.05$) and provided their progeny with less care (parental care; $F_{1,20} = 5.82$, $P = 0.03$). Pacey and Marsh (1998) and Marsh and Pacey (in press) also found that nonnative fishes of the Lower Colorado River provided more care to their young than native fishes in that ecosystem. Native fishes tended to use more seasons throughout the year to spawn, whereas nonnative fishes had shorter and more defined spawning periods (spawning seasons; $F_{1,20} = 6.81$, $P = 0.02$). In addition to the ecological characteristics we reviewed here, native and nonnative fishes in the southwestern United States differ in that maintenance of natural flow regimes is key to the sustainability of native fishes, although it is not required for nonnative fishes (Rinne et al., in press).

This comparison of species characteristics between native and nonnative fishes provides some insight into developing control strategies for nonnative fishes in the Gila River basin. Some habitats (i.e., lentic areas and areas with temperatures too high for native species) may be more appropriate for control measures because of differential selection between native and nonnative fishes. Similarly, control measures may be more effectively applied at particular life stages because of differential vulnerabilities (e.g., prolonged period of parental care by nonnative fishes as compared with native fishes). Although prolonged spawning periods by native species suggest that a control program for nonnative species may also affect the most vulnerable life stage (young of year) of native species, it also suggests that native fishes may have the opportunity to successfully spawn after a control event. In addition to using ecological differences between native and nonnative fishes to more effectively reduce or eliminate nonnative fishes, knowing the distribution of each species could also be used to selectively control nonnative species.

Information on the distribution of native and nonnative fishes in the Gila River basin can be used to identify areas inhabited solely by native or nonnative species, or to identify key intersections between these groups. The Arizona State University Lower Colorado basin geographic information system fish summary database (http://www.peter.unmack.net/gis/fish/colorado) was used to determine the distribution of native and nonnative fishes. This database included data through 2001 for native and nonnative fishes and summarized species occurrence by major and minor drainages. The sources for the database included museum specimens, primary and gray literature, and the Arizona Game and Fish Department Nongame Branch database.

This database revealed several patterns of distribution between native and nonnative fishes of concern. Most areas within the Lower Colorado River basin where native fishes still exist without nonnative fishes occur in the Gila River basin (Figure 2-1). In addition, virtually all of the Colorado River and many of the tributaries of the Gila River had native and nonnative fishes. While this coarse scale of range overlap between native and nonnative species can indicate general patterns in distribution, the overlap of particular species within reaches will be important

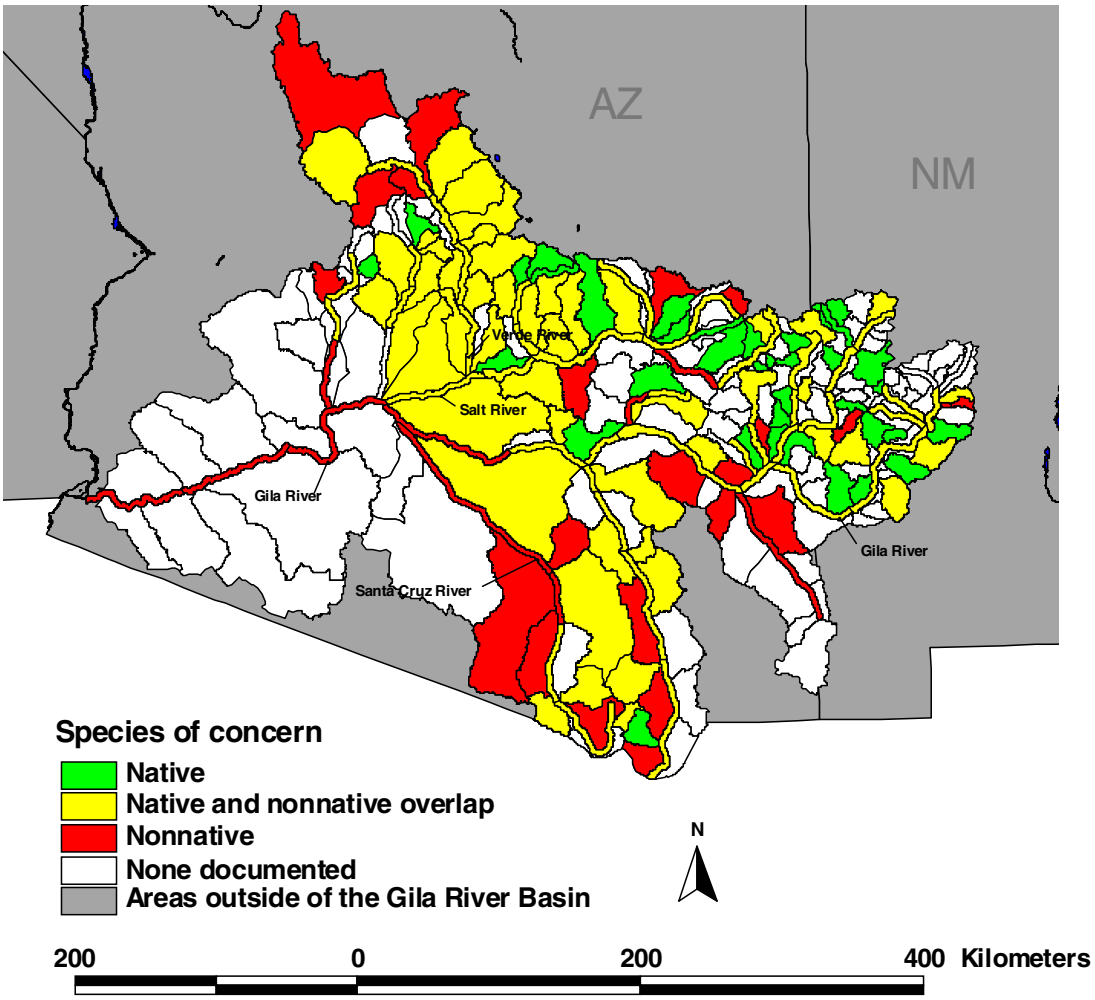


Figure 2-1. Map depicting the distribution of native and nonnative fishes of concern in the Gila River basin using records current through 2001 (Table 2-1).

in developing a control program for nonnative fishes. Examining the overlap of particular native and nonnative species indicates the scope of the problem nonnative fishes pose for imperiled native species and can serve as a starting point for risk assessment. For example, the complete spatial overlap between the native Gila topminnow and the nonnative mosquitofish (Figure 2-2) combined with the knowledge that the mosquitofish is a key threat to the Gila topminnow (Schoenherr 1977) suggests a critical need to implement conservation measures.

While data on life-history characteristics, environmental tolerances, and distribution of native and nonnative fishes do not provide a solution to controlling nuisance fishes, they could, when used as a means to focus control measures (such as the use of chemicals), be used to identify critical life stages, habitats, or geographic areas that might be most appropriate for control.

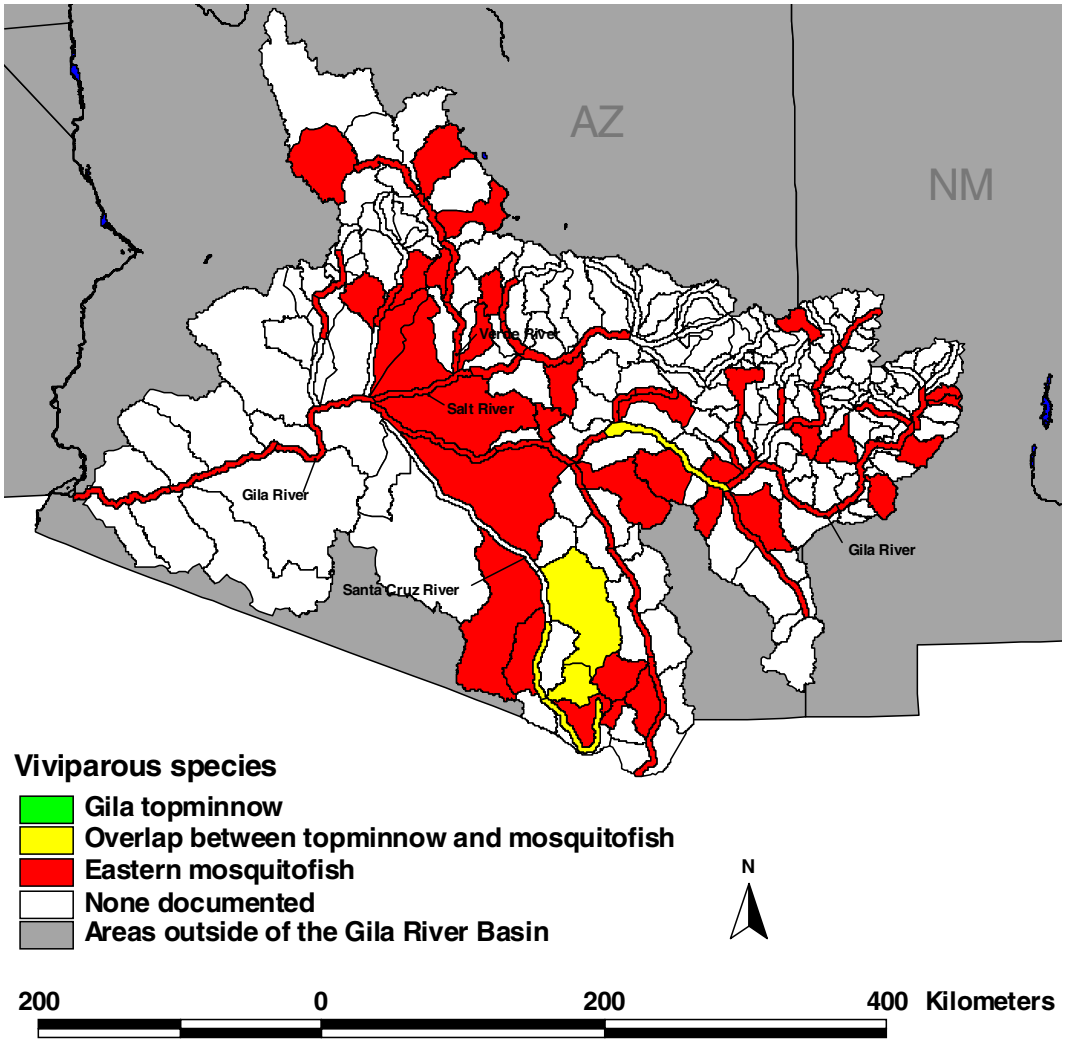
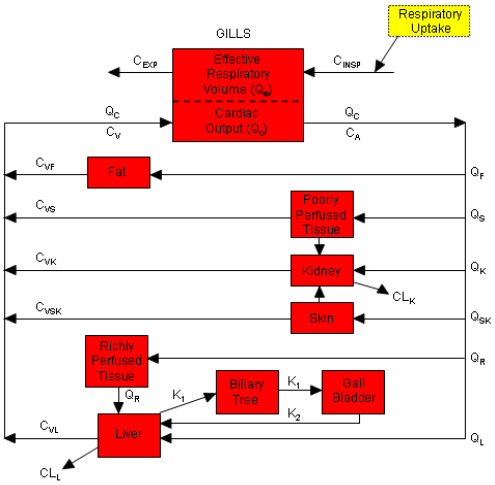


Figure 2-2. Map depicting the complete spatial overlap of the native Gila topminnow and the nonnative mosquitofish.

Chapter 3. General Considerations for Understanding the Actions of Selective Toxicants



by William H. Gingerich and Guy R. Stehly

Today there are literally millions of known chemicals; their origin being either synthetic or natural. The Chemical Abstract Service Registry contains records for more than 21 million organic and inorganic substances with about 4,000 new chemical structures being added daily (http://www.cas.org/casdb.html). In contrast, the Registry of Toxic Effects of Chemical Substances listed 139,704 entries of chemicals with known toxic properties, less than one half of one percent of all known chemicals (http://www.cdc.gov/niosh/97-119.html). Of those chemicals, only a small subset are used specifically because they are toxic to living things. These chemicals find applications as pesticides, herbicides, parasiticides, microbicides, fungicides, and antibiologicals including antimicrobials and chemotherapeutic agents. In the broadest sense, these commercially applied chemicals have been developed specifically because of their toxic properties to some living system. Some chemicals demonstrate modest selective toxicity between closely related organisms. In general, selectivity is most commonly observed between phylogenetically divergent organisms. It is more common to find selective chemical toxicity between plants and animals, or between animals and microorganisms than it is to find selectivity among closely related animals, such as a mouse and a rat (Albert l985). However, there are examples of selective toxicity between closely related organisms. As examples, males and females of the same species are differentially sensitive to some drugs, and there are differences in some drug sensitivities between human races (Lennard 1993). The specific factors that confer selective toxicity between different animal species are only now becoming understood.

In this chapter, the concept of receptors and receptor responses will be presented followed by several general causal mechanisms that help explain the basis of selective toxicity. The chapter provides an overview of the potential usefulness of models of drug kinetics in animals and the potential usefulness of pharmacokinetic models of toxicants including physiologically based pharmacokinetic (PBPK) models to serve as screening tools to identify selective piscicides.

3.1 Receptors and Drug/toxicant Action in Organisms

The principles and general concepts of toxicology are founded in the understanding of drug actions on biological systems that have been developed for pharmacology, the science of drug action on biological systems. Indeed, toxicology is still considered a subset of the overarching science of pharmacology, and, therefore, the concept of drug and toxicant effects are closely aligned. Most drugs are designed to facilitate a particular function within an organism and may act to either speed up or slow down a process or make more or less of a critical reactant in a biochemical pathway. Given in excess, drugs can produce unwanted effects that can be toxic.

Toxic agents produce effects to the extreme such that the survival of the organism is jeopardized. However, given in lower doses, even toxic agents can produce beneficial effects.

An example is the now routine cosmetic use of the potent nerve poison botulinum toxin, Botox, to reduce some of the effects of aging. At the extreme end of the toxic spectrum of chemicals are those intentionally applied biological poisons, i.e., pesticides that are used to kill a specific group of target organisms. The key to understanding how toxicants may be selective is derived largely from an appreciation of the interaction of toxicants with specific biological elements called receptors.

The biological effects of chemical exposure are considered to be mediated by the interaction of the chemical with specific endogenous biological components termed receptors. This interaction serves as the basis for discussing selective toxicant design and structure-activity relationships of toxicants.

Operationally, a receptor may be defined as a macromolecular element of an organism, which when combined with a complementary endogenous chemical agent (ligand), acts to control, regulate, or otherwise enable critical biological functions in the organism (Ross 1995). Interactions of the chemical ligand with the receptor generally involves most known types of chemical bindings including covalent, ionic, and hydrogen bonding, as well as van der Waals and hydrophobic interactions (Ross 1995). Receptors currently are considered to function in two ways. First, the receptor defines a binding domain or specific three-dimensional configuration that sterically accommodates a variety of complementary ligands of roughly similar physicochemical properties. Second, the receptor-ligand complex results in a defined array of subsequent effects, in essence an effector domain, that results in a particular biological effect or constellation of effects (Ross 1995). The biological consequences resulting from the receptor-ligand interaction may vary from tissue to tissue within the organism. By this model, it has been possible to explain the observable diversity of structure-activity relationships in living organisms by two means. First, it allows for the possibility that a number of diverse receptors and diverse ligands can interact to produce binding complexes that result in effects by similar or common biochemical pathways. Second, the model allows for the possibility that a single chemical ligand can bind to a variety of structurally unrelated receptors to produce a variety of resultant binding complexes that act to produce a different effect by independent and unrelated mechanisms (Ross 1995). This is a critical concept in considering mechanisms of selective toxicity since biochemical diversity may form the basis of some selectivity to organisms.

The majority of receptors are proteins. Examples of receptor macromolecules are those for endogenous chemicals, such as hormones, growth factors, neurotransmitters, and a variety of enzymes that regulate metabolic, regulatory, or neuronal functions (Ross 1995). The effects of exogenous chemical ligands on the receptor-ligand effector domain can be either to enhance or impair the normal endogenous chemical/receptor interactions. Chemicals that mimic or enhance the effects of endogenous chemical agents are termed agonists; those that retard or block an effect are termed antagonists. The agonistic action of many pharmaceuticals is to supplement or support an existing biological ligand that has been reduced or degraded by pathological processes, genetic deficiencies, or aging. Conversely, the antagonistic actions of many chemical toxicants are to inhibit, either reversibly or irreversibly, biological processes important to support critical life functions. Clearer understandings of receptor structure and function have formed the basis for new drug discovery through structure-activity relationships between the receptor and agonistic or antagonistic ligands (Kuntz 1992) and will serve in this report as a science-based tool to identify new potential candidate piscicides.

3.2 Basis for Selective Toxicants

Concerning the discovery and development of taxon selective piscicides, it is unlikely that purely physicochemical differences in primary receptors are sufficiently great among

phylogenetic classes of fish to account for the perceived differences in toxicity that are known for piscicides. It is more likely that the selectivity is the product of both differences in the expression of biochemical response to toxicants between species and differences between species in the rates and routes by which sensitive receptor sites are occupied by the toxicant. A generalized overview follows of several factors thought to contribute to the basis for selectivity of toxicants to different species—comparative biochemistry and comparative toxicant distribution.

Comparative Biochemistry

Most organisms persist in their environments by taking in food, converting that food to energy and using the derived energy to perform basic life tasks, such as mobility, growth, and reproduction. These processes are facilitated by a number of basic biochemical pathways and are regulated by the action of critical branch point enzymes that act to limit flow of substrates down individual key pathways. While most of the biochemical pathways are similar among organisms and their functions highly conserved, individual groups of organisms may use one pathway over another because of unique life-history requirements. In general, the greater the phylogenetic difference between the organisms, the greater the difference in the use pattern and integration of the particular pathways. Differences in the expression of these pathways may lead to the basis of selectivity. Selectivity may be achieved by using a specific inhibitor ligand to block one vital biochemical pathway used exclusively by a particular animal group.

Poikilothermic organisms must adapt to a diverse variety of abiotic factors if they are to persist. For temperate freshwater animals, accommodation to changing temperatures presents an important challenge. Freshwater fish in temperate to subarctic latitudes have evolved a number of molecular mechanisms to compensate to changes in temperature to maintain relatively normal physiological processes in the face of rising or falling temperatures (Hochachka and Somero 1971, Hazel and Prosser 1974). Differences in the strategies taken by individual groups of poikilotherms to adapt to fluctuating abiotic factors, either seasonally or in specialized areas, characterized by rapidly fluctuating physical environments may make one group more susceptible than another to a toxicant at a particular critical time. These different adaption strategies, then, may serve as the basis for a species selective treatment with a toxicant.

Comparative Toxicant Distribution

A unifying principle in quantifying the response of an animal to an exogenous chemical is that the responses are generally based on the concentration of the chemical delivered to the appropriate receptor(s) and the time it takes for a critical number of receptors to form a receptor-ligand complex. Differences in the degree of physical access of the chemical to common receptors between different organisms can be a powerful determinant of selective toxicity. A model depicting factors that affect delivery of a chemical ligand to cellular receptors is presented in Figure 3-1. A mathematical representation of the model could be made as a series of differential equations of the change between free and bound drug concentration available in each of the several levels of biological organization over time. The rates of change are dependent both on the concentration of free chemical in the system and the tenacity with which the drug is bound to storage or binding ligands that are not the drug receptor.

Figure 3-1 shows that the important factor in eliciting a response is the number of ligand-receptor complexes formed. In many instances, the ligand is loosely bound to the receptor and is free to disassociate. Therefore, the concentration of free ligand that remains in the immediate vicinity of the receptor population is a factor in determining the magnitude and length of the drug response. For the free ligand to reach sufficiently high concentrations at the receptor site, a

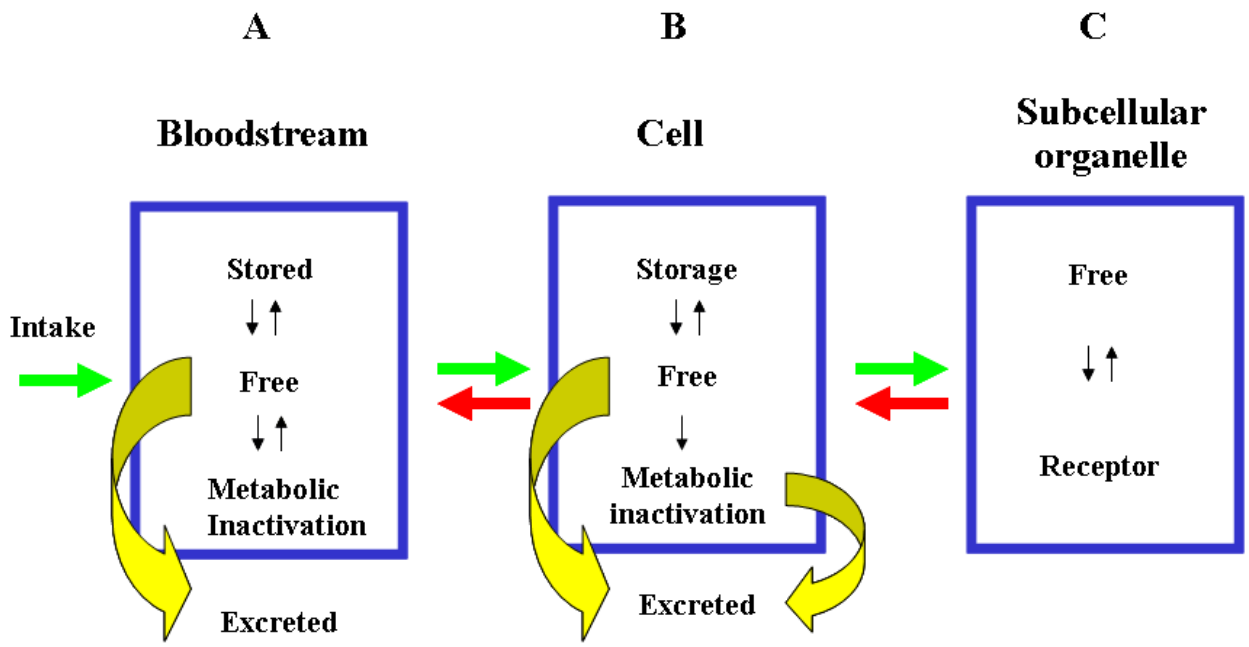


Figure 3-1. Some of the physicochemical factors that control the transport of a chemical ligand to a receptor. Opposing arrows suggest equilibrium conditions between and among different physiological spaces (*boxes*) while the equal sizes of the arrows denote similar rates of transfer into and out of each space. Spaces are separated by membranes. Diffusion across the membranes may be by simple diffusion driven by differences in the concentration gradient of the chemical ligand on either side of the membrane, facilitated diffusion that requires a transporter molecule to assist the ligand across the membrane but does not require energy, or active diffusion against a concentration gradient and driven by metabolic energy. Transfer of chemical in and out of each compartment may occur at different rates and thereby increase or reduce the concentration of the chemical transferred into or out of a compartment. At intake, the chemical enters the bloodstream (*A*) where it is distributed throughout the organism. The concentration of free chemical in the blood drives the equilibrium into the next space and is controlled by the amount of chemical ligand reversibly stored in inert storage sites such as plasma proteins and the amount of ligand inactivated either by metabolism or excretion. Free ligand in the bloodstream diffuses to individual cells (*B*) where it again can be held in an inert state at storage sites or reduced by cellular metabolism and/or excretion. Finally, a portion of the intracellular free chemical is available to diffuse into a subcellular organelle (*C*) where it is available to interact with a receptor to produce an effect.

series of generally reversible reactions are likely to occur between the ligand and the storage or transport molecules that distribute the ligand throughout the body. Metabolism of the parent ligand to a form that is not compatible with the receptor is another mechanism by which the concentration of free drug reaching the receptor population is reduced. However, most drugs with distinct pharmacological characteristics act only in a specific manner and only in tissues that are susceptible to the chemical; i.e., those that have a specific ligand-receptor effector domain.

Uptake, distribution, and elimination of chemicals by fish depends greatly on the physicochemical properties of the chemical and includes the degree of lipophilicity, generally expressed as the differential solubility between n-octanol and water or the octanol-water partition coefficient (Neely 1979). Because fish are essentially continuously exposed to chemicals in water solution, a chemical with a favorable n-octanol/water partition coefficient is generally conceded to enhance uptake and bioaccumulation in fish (Veith et al. 1979).

Physicochemical properties that enhance rapid uptake and distribution are considered a positive attribute for candidate piscicides.

Uptake of waterborne chemicals by fish is generally conceded to be primarily across the thin respiratory membranes of the gills. The gills are the primary regulating surface between the external water medium and the fish's internal medium. As such, the gill functions in a variety of capacities as a respiratory surface area, a site of active ion exchange, and a site for excretion of nitrogenous wastes. The significance of the gill as a site of uptake of waterborne chemicals is that virtually all circulating blood passes through the gill.

At least three vascular networks have been identified in the gill: (1) a respiratory pathway, (2) a nutrient pathway for branchial tissues, and (3) an interlamellar pathway reminiscent of mammalian lymphatic capillaries (Olson 2002*a*). Gill circulation is complex and appears to be controlled by a variety of neurocrine, endocrine, and autocrine signals (Olson 2002*b*). The general complexity of the system suggests that it may be a likely site for differential toxicity among fish, particularly since different groups of fish with different physiological requirements may be able to modify their blood exposure to the water by increasing or decreasing the functional water/blood surface area of the gill for gas exchange (Burggren et al. 1979, Hughes 1980, Nimi and Morgan 1980), thereby also altering the functional gill area for uptake of toxicant. There is some evidence that the lamprey-specific toxicants 3-trifluoromethyl-4-nitrophenol (TFM) and 2-aminoethanol salt of 2',5-dichloro-4'-nitrosalycylanilide (Bayluscide®), both weakly acidic organic molecules, act specifically to damage branchial organic anion transport cells in sea lamprey gills (Mallatt et al. 1985, 1994). The sensitivity of these cells in the sea lamprey has been suggested to be the basis of the selectivity of both chemicals for sea lamprey. Others have found that a partial explanation of the relative sensitivity of lamprey to TFM and Bayluscide® is that, unlike higher bony fishes, lamprey lack adequate activity of the enzyme glucuronyl transferase that acts to detoxify both chemicals by secondary conjugation with a glucuronide moiety (Lech and Statham 1975). It is likely that most of the selectivity observed in the classes of toxicants that have been developed for fishery management purposes is the result of differences in how the chemicals are taken up, distributed, metabolized, and eliminated by the individual organisms.

Predicting Selective Chemical Toxicity Based on Pharmacokinetic Models

One of the principal mechanisms for the selective toxicity of pesticides to undesirable species compared with desirable species concerns differences in the distribution (i.e., pharmacokinetics) of the compound among species (Albert 1985). Differences in absorption, distribution, and excretion can account for differences in toxicity. Further, the relative ability of a species to absorb, distribute, or excrete compounds can sometimes be predicted on the basis of knowledge of anatomical and physiological differences in the species.

The field of pharmacokinetics studies the time course of chemical absorption, distribution, metabolism, and excretion by an organism (Gibaldi and Perrier 1982). A common method of characterizing the pharmacokinetics of a compound in pharmacology and toxicology is to follow the concentration of a chemical within the blood or plasma through time after administration. Based on knowledge of concentration of the drug in the plasma, information can be inferred on its distribution in other tissues.

Pharmacokinetic models, mathematical characterizations of a drug or foreign chemical in the body of an organism, are used to describe the relationship between the concentration of the compound in blood or plasma over time. The data are fit to several possible model equations that describe the disposition of the compound; the one that best fits the data is determined.

These models are referred to as compartmental models because the chemical is said to act as if the organism was made up of one or more compartments (Figure 3-2). Most common compounds display characteristics as if they were distributed among two or three compartments.

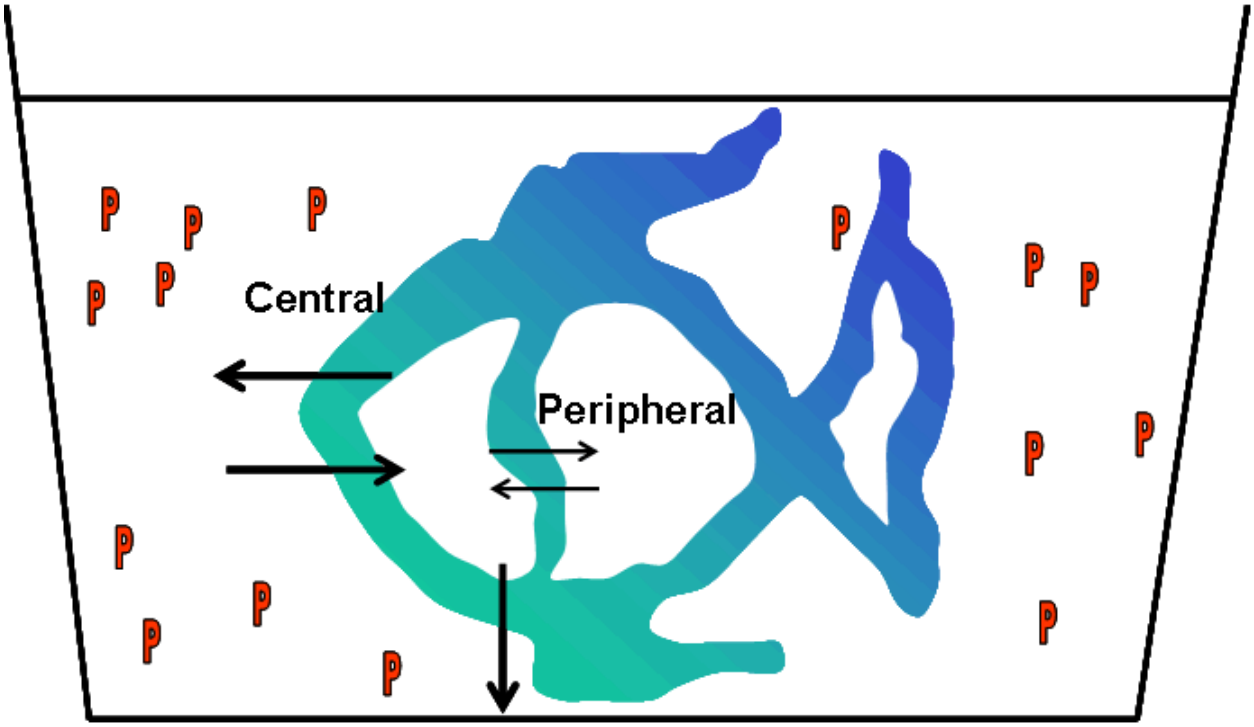


Figure 3-2. A two-compartment pharmacokinetic model for a piscicide in fish. Piscicide (*P*) enters the central compartment where it can exit unchanged, be metabolized (*bold arrows*), or enter a peripheral storage compartment (*lighter arrows*).

The plasma and well-perfused tissues represent one compartment (referred to as the central compartment) where elimination occurs. Tissues with less perfusion, such as fat and muscle, comprise a second or third compartment (peripheral compartment) where the compound is stored until transferred to the central compartment where it can be eliminated. With fish that are too small for multiple blood sampling, pharmacokinetics of a compound can be characterized on the basis of concentrations of parent compound and metabolites in the whole body of the fish and in the water used for waterborne exposure (Stehly and Hayton 1989). These models are similar to compartmental models on the basis of plasma concentrations of the compound, but they are fit simultaneously to data for concentrations of the compound in the fish and water.

Theoretically, registered or proposed piscicides used in fishery management could be evaluated to determine if distributional or elimination characteristics account for species differences in toxicity. It may then be possible to predict pharmacokinetic characteristics resulting in greater toxicity to a particular species. This strategy relies on the chance finding of a piscicide that is more toxic to a target invasive species than to nontarget species. A number of residue studies have been conducted on compounds currently registered with the EPA or with candidate fishery management chemicals. These studies were not designed to determine pharmacokinetics of the compound in a fish species. If this information was developed, pharmacokinetic models could then be used to predict plasma concentrations. Since this information has not been developed for

any species of fish, evaluation of differences between native and nonnative fish species cannot be made yet.

Although compartmental pharmacokinetic models are relatively easy to develop, their results cannot be extrapolated to different species, dosages, or other factors that may change the distribution or elimination of the compound. Piscicides would probably be used at a particular dose and therefore, as with development of many human pharmaceuticals, extrapolation of dosage may not be particularly important. Compartmental models, however, would still have limited usefulness in extrapolation to other species and conditions.

More complex models based on the specific physiology of the individual species and physicochemical characteristics of the compound can and have been used to allow for better predictive capability on chemical disposition within an organism. These models, known as PBPK models, have been used most often for risk assessment of toxicity in humans on the basis of laboratory studies in animals, such as rats and mice. These models are generally composed of a number of compartments that are important to describe the disposition of a chemical (Figure 3-3). The compartments defined in the model include the central compartment (e.g., well-perfused tissues), storage compartments (e.g., poorly perfused tissues, such as adipose tissue), elimination compartments (e.g., liver, kidney), and for fish, the gills that may be important for uptake and elimination of compounds.

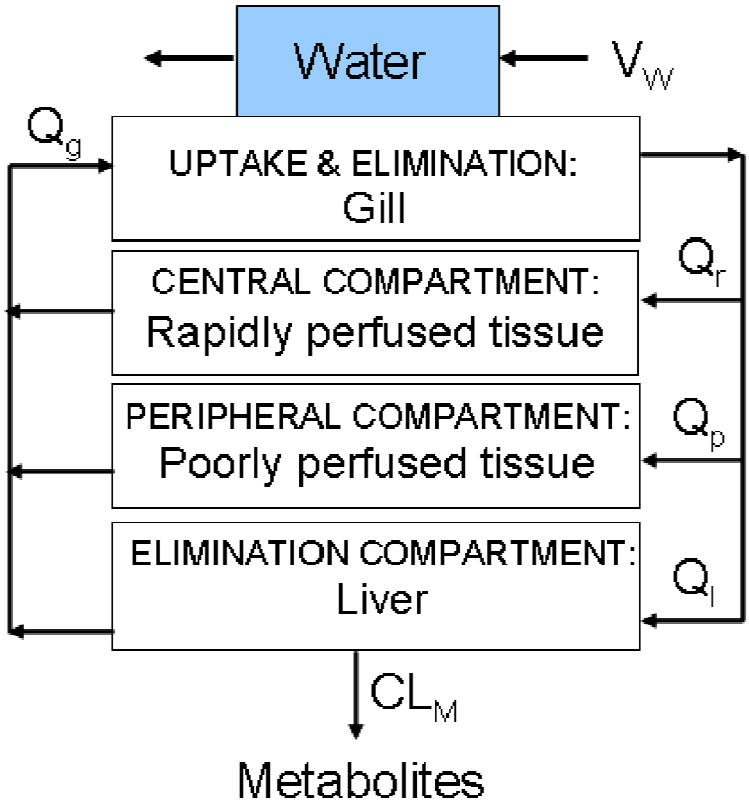


Figure 3-3. A simple physiologically based pharmacokinetic model for fish with a component for transfer of a chemical between the water and fish through the gill, a compartment composed of tissues with a relatively large perfusion of blood, a storage compartment (poorly perfused), and an elimination compartment (liver) that produces metabolites of the chemical. Arrows denote blood flow among tissue groups (Q_g, Q_r, Q_p, Q_l), flow of water through the gills (V_W), or metabolic clearance from eliminating organs (CL_M).

Physiologically based pharmacokinetic models require a large amount of data that must be obtained from the literature or experimentally, including physiological variables (i.e., clearances and metabolism), transport variables (i.e., absorption, permeability), thermodynamic variables (i.e., tissue/blood partition coefficients), and anatomical values (i.e., blood flows, tissue volumes; Lutz and Dedrick 1985). The PBPK models are considered superior to simpler compartment models because they can provide an exact description of the time course for the compound in any organ or tissue within the body and are based on the physiology of the animal. Additionally, any biological process important to chemical disposition that can be described mathematically can be incorporated into the model. Because these models are based on anatomy and physiology, they are useful for extrapolation to other doses, species, and conditions affecting physiology (e.g., increased respiration). The PBPK models have been used to interactively determine the most appropriate experiments to validate the model (Conolly et al. 1999). More recently, the kinetics of individual compounds in chemical mixtures were interactively evaluated. This evaluation provided an alternative to the large number of possible experiments required to test interactions of chemical mixtures. The authors termed the computer modeling as "in silico" toxicology (Dobrev et al. 2002).

Although there is interest in using physiologically based pharmacokinetic models to assist in developing data to support registration of pesticides and pharmaceuticals, this method has not been applied successfully to date. Efforts are currently under way in the pharmaceutical industry to approve new pharmaceuticals using PBPK modeling to develop preclinical data. Efforts also have been made to predict partition coefficients of chemicals between tissues and plasma on the basis of chemical characteristics and physiological make up of tissues rather than to experimentally collect these data. The U.S. Food and Drug Administration (FDA) is expecting that drug sponsors will submit data in the form of PBPK models in support of clinical trials (Peter Lee, FDA, personal communication). Scientists at the Upper Midwest Environmental Sciences Center (UMESC) have also proposed use of the crop grouping concept to support the idea of multiple fish species approvals for aquaculture drugs partly on the basis of use of PBPK models (Gingerich et al. 1998). The crop grouping concept hypothesizes that fish can be grouped or data normalized concerning depletion of drug residues on the basis of phylogeny, thermodynamics of the residue or temperature related activity differences among different fish species. This could result in satisfying FDA data requirements in residue depletion for multiple species of fish on the basis of testing a few surrogate fish species. The FDA has acknowledged use of pharmacokinetics to support crop grouping, but does not specifically limit it to use of PBPK models (FDA 1999).

Physiologically based pharmacokinetic models have been used to describe the disposition of a limited number of chemicals in fish for compounds such as chlorethanes, pyrene, and an organophosphate pesticide (Law et al. 1991, Nichols et al. 1993, Abbas and Hayton 1997). One problem with using these models to extrapolate among species of fish is the lack of basic information on physiological differences among species, in particular ventilation at the gill, blood flows to tissue groups, and relative volumes of tissue groups.

In summary, pharmacokinetic data have not been developed for registered or potential piscicides that would allow comparison of their disposition between native and nonnative fishes. Development of PBPK models in fish is in its scientific infancy, few data are available on physiological differences required for the models in fish species, and these models are only now being considered to develop medicinal drugs. Although PBPK models could conceivably be used to develop species-specific piscicides, cost requirements to identify these compounds is probably greater than direct testing of the chemicals species by species and therefore use of PBPK models to identify species-specific piscicide is premature at this time.