Future Fish

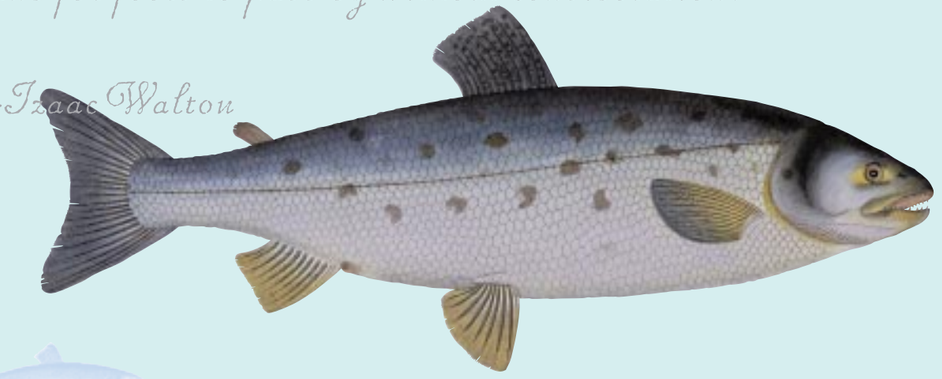
Pew Initiative on Food and Biotechnology

Future Fish

Issues in Science and Regulation of Transgenic Fish

"Rivers and the inhabitants of the watery elements are made for wise men to contemplate and for fools to pass by without consideration."

-Izaac Walton



A Report Prepared for the Pew Initiative on Food and Biotechnology

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Preface

Recent applications of genetic engineering have led to the development of genetically modified (GM) fish for aquaculture. Endowed with characteristics such as faster growth or disease resistance, these fish offer the prospect of more efficient and less expensive production. Government agencies in the United States and other countries are now reviewing proposals to regulate and market genetically modified fish. As a result, fish may be the first genetically modified animal to come to the U.S. dinner plate.

This report provides an overview of the issues surrounding transgenic fish. The report reviews the development of aquaculture biotechnology, the status of current research, its potential economic, environmental, and other benefits, its possible food safety and environmental risks, and the application of current U.S. laws and regulations as it moves to commercial development. While the report does not contain specific policy recommendations, it highlights a number of key regulatory issues for policymakers.

Demand for seafood, particularly among developed nations, has increased dramatically in recent years. In many areas, however, increased demand has led to unsustainable overfishing and the collapse of open access fisheries. Aquaculture, the farming of aquatic organisms in managed environments, has met part of the demand. Worldwide aquaculture production has more than doubled in ten years, producing 25.5 million metric tons in 1994 with a value of about $40 billion.

The growth of aquaculture has not been without environmental controversy. Concentrated fish pens can generate large amounts of waste and pollutants. The demand for fishmeal (aquaculture feed processed from captured fish) may increase pressure on capture fisheries and lead to a net loss of fish protein. The escape of domesticated varieties of farmed fish from open net pens can threaten wild fish populations by interbreeding or becoming established as an invasive species.

Some scientists and environmentalists are concerned that introducing genetically altered fish into the equation will add to the environmental concerns associated with conventional aquaculture. The possible environmental impacts of genetically modified fish do not differ in kind from those of traditional aquaculture fish. However, adding genetic traits not likely to occur in nature raises the concern that it may make transgenic fish more

likely to survive if they escape, and therefore more likely to affect wild fish populations by interbreeding or by becoming an invasive species. Limited science makes it difficult to predict the probability of the many scenarios researchers have hypothesized or to assess in advance the environmental consequences, which could range from benign to adverse. If escapes did occur and the consequences were undesirable, however, it would be difficult, if not impossible, to "recall" the escaped transgenic fish. To reduce these risks, developers of transgenic fish are perfecting existing methods and developing new ones to sterilize these fish to prevent them from spreading their transgenes to wild fish.

A patchwork of federal laws address the environmental issues raised by conventional aquaculture and spread fragmented authority among different federal agencies. For example, the U.S. Environmental Protection Agency deals with water pollution issues posed by aquaculture facilities, while the Army Corps of Engineers considers environmental impacts as part of the process for issuing permits for aquaculture facilities in navigable waters. But no federal agency appears to have clear legal authority to regulate aquaculture facilities to avoid potential harm to wild fish communities, unless the wild fish are already threatened or endangered under the Endangered Species Act. Indeed, federal authority in this area is limited; the primary regulatory responsibility for fisheries and aquaculture resides at the state level.

The advent of transgenic fish adds a layer to this already complex regulatory regime. Federal policy, developed in the mid-1980s, treats biotechnology products no differently than products produced in more conventional ways. However, as biotechnology continues to develop, new applications raise questions as to what kind of "product" they are—and therefore which federal law applies.

In the case of transgenic animals, including fish, the Food and Drug Administration (FDA) has indicated its intention to regulate them as "new animal drugs" under the Federal Food, Drug and Cosmetic Act (FFDCA) because the genetic construct used to create transgenic animals falls within the statutory definition of a "new animal drug." As a result of this interpretation, developers cannot grow or sell transgenic fish until the FDA first has found that the fish are "safe and effective" as defined by the FFDCA.

The FDA's intention to regulate transgenic animals (including fish) under the FFDCA's new animal drug approval provisions illustrates some of the challenges in applying existing authority to new biotechnology products. On the one hand, using the new animal drug approval process allows regulators to ensure that transgenic animals such as fish are safe to eat before they come to market. On the other hand, there is significant legal uncertainty about the scope of FDA's authority under the new animal drug laws to deny approval or impose restrictions on the basis of potential environmental impacts that do not directly affect the health of humans or of the transgenic fish itself—such as impacts on wild fish species. In addition, the new animal drug approval process provides very little opportunity for notice or public participation; indeed, the very existence of an application for approval remains confidential unless disclosed by the applicant. As the FDA has itself acknowledged, the procedures make it difficult to have the kind of open process required for environmental assessment. Finally, it is difficult to know how the rules that apply to proving the safety and efficacy of traditional animal drugs will apply to transgenic animals, creating uncertainty for both industry and the interested public. The FDA, policymakers, industry, and the public interest community need to address these issues.

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Michael Rodemeyer
Executive Director
December 2002

chapter

ONE

Development, Status, and Economic Implications

chapter 1

DEVELOPMENT, STATUS, AND ECONOMIC IMPLICATIONS

A INTRODUCTION

The first reports of the application of modern biotechnology to animals appeared in the 1980s. Genetic engineers inserted novel genes into mice, rats, pigs, and fish to achieve faster growth rates, improved resistance to disease, and other effects. Although some of these traits were attainable through traditional breeding methods, genetic engineering can produce greater (or more dramatic) effects while expanding the range of potential traits. In 1983, the cover of *Science*, one of the most widely read scientific journals in the United States, sported a photo of a huge mouse bearing novel genes that accelerated its growth rate (Palmiter et al. 1983). Shortly after, scientists in China reported the first successful insertion of novel growth hormone genes into fish. These events stirred substantial debate and captured the interest of biochemists, geneticists, aquaculture scientists, and private entrepreneurs, leading to more transgenic research in laboratories around the world, some of it focusing on fish and other aquatic organisms.

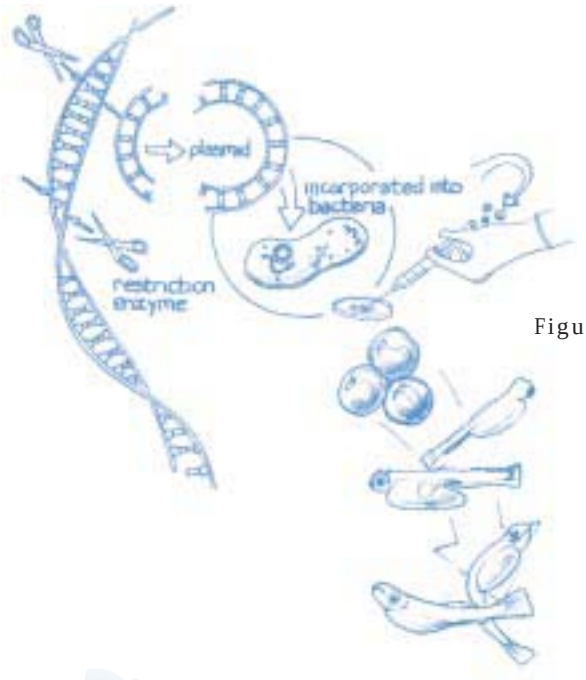


Figure 1: **How a Transgenic Fish Is Created**

In the broadest sense, genetic modification can refer to changes in the genetic makeup of organisms not found in nature, including hybrids (offspring of parents from different species or sub-species). This report focuses on transgenic fish, where scientists use recombinant DNA techniques to insert genetic material from one organism into the genome of a fish or other aquatic organism.

Following these early demonstrations of the ability to genetically modify animals, research and development of aquatic genetically modified organisms (GMOs) expanded rapidly. Aquatic animals, particularly fish grown in aquaculture systems, attract significant research attention for two primary reasons. First, fish lay eggs in large quantities and those eggs are more easily manipulated, making it easier for scientists to insert novel DNA into the eggs of fish than into the eggs of terrestrial livestock. (In comparison, cows and pigs produce fewer eggs at a time, and once scientists insert novel DNA, they must re-insert the altered eggs into the animal.) Second, aquaculture is one of the fastest growing food-producing sectors globally, suggesting growing demand for more aquaculture products. Since 1984, commercial aquaculture has expanded at an annual rate of almost 10 percent, compared with a 3 percent growth rate for livestock meat and a 1.6 percent rate of growth for capture fisheries[1] (FAO 2000). While the growth has been concentrated in Asia (Inland Water Resources and Aquaculture Service 1997), aquaculture is also one of the fastest growing sectors of U.S. agriculture, with the total value of products sold increasing from $45 million in 1974 to over $978 million in 1998 (National Agricultural Statistics Service 2000). In fact, commercial aquaculture sites produce nearly all of the catfish and trout and about one-half of the shrimp and salmon grown in the United States (Goldburg, 2001).

The Food and Agriculture Organization of the United Nations reports that close to 100 million metric tons of fish are consumed worldwide each year. Consumption of fish and its relevance to national diet, however, varies between countries. Developed countries generally consume more than developing countries. Japan, for instance, has some of the highest per capita consumption levels while Africa and the Near East have some of the lowest (Westlund, 1995). Meeting the demand for seafood will likely require a number of steps including, but not limited to, continuing increases in aquaculture production, restoring depleted capture fisheries,[2] maintaining currently productive ones, and assuring sustainable practices in any newly developed fisheries (Marine Stewardship Council 1998, Peacey 2000).

[1] Discussions of seafood production often distinguish capture fisheries, which harvest fish from natural waterways, from aquaculture, which grow fish in net pens or tanks.

[2] Fish obtained through capture fisheries are often used as feed for fish raised in aquaculture fisheries. In fact, scientists estimate that 1.9 kilograms of captured fish are used to produce every kilogram of farmed fish (Naylor et al. 2000).

TABLE 1

World fisheries production and utilization

PRODUCTION	1994	1995	1996	1997	1998	1999*
			(million tons)			
Total inland	18.8	21.4	23.4	25.1	26.7	28.0
Total marine	93.4	94.8	96.9	97.3	90.4	97.2
Total world fisheries	112.3	116.1	120.3	122.4	117.2	125.2
Total capture	91.4	91.6	93.5	93.6	86.3	92.3
Total aquaculture	20.8	24.6	26.8	28.8	30.9	32.9
UTILIZATION						
Human consumption	79.8	86.5	90.7	93.9	93.3	92.6
Reduction to fishmeal and oil	32.5	29.6	29.6	28.5	23.9	30.4
Population (billions)	5.6	5.7	5.7	5.8	5.9	6.0
Per capita food fish supply (kg)	14.3	15.3	15.8	16.1	15.8	15.4

*Preliminary estimate.

(FAO 2000)

Today, fish are poised to become the first genetically modified animal organism grown for human food. Although to date, such fish are not commercially available in the U.S., researchers have genetically modified at least fourteen species to enhance their growth. These species include several varieties of carp, trout, and salmon, as well as channel catfish, loach, tilapia, and pike. Consequently, government agencies in the U.S., Canada, and Cuba are now reviewing proposals for commercialization of genetically modified fish. In China, scientists conducting food safety studies will soon seek government approval to introduce two lines of transgenic carp, one of which contains a salmon growth hormone (Zhu 2001, Li 2001).

Examples of Transgenic Aquatic Organisms in Research, Development, or Commercialization

TABLE 2

SPECIES GROUP	POTENTIAL BENEFITS	INTENDED END USE OF MODIFIED ORGANISM	PRODUCT STATUS
Finfish US & European patents	Increased growth rate and food conversion efficiency in Atlantic salmon by inserting chinook salmon growth hormone gene that is switched on year-round, thereby fostering year-round, rather than mainly summer, growth.	Human consumption	Seeking Regulatory Approval of Product Method has been patented; FDA is reviewing application for commercial use
Canadian & US research	Increased growth rate and food conversion efficiency in rainbow trout via insertion of sockeye salmon growth hormone gene.	Human consumption	Research Being used as a model for other research
Cuban research	Increased growth rate and food conversion efficiency in tilapia after insertion of tilapia growth hormone gene linked to a promoter sequence from the human cytolomega virus (CMV).	Human consumption	Seeking Regulatory Approval of Product
Chinese research	Improved disease resistance in grass carp by inserting a human interferon gene.	Human consumption	Research
Chinese & Canadian research	Increased cold tolerance in goldfish by inserting the ocean pout antifreeze protein gene.	Ornamental, feed and research purposes	Research
UK & US research	Production of clotting factor within tilapia after insertion of human gene for clotting factor VII, for medicinal applications.	Pharmaceutical production	Research
US research	Increased growth rate and non-specific bacterial immunity in channel catfish using salmon growth hormone genes and cecropin genes from a moth, respectively.	Human consumption	Research
Mollusks US Patent	Improved disease resistance and growth acceleration potential in mollusks by harnessing altered genetic material from a virus to introduce foreign DNA.	Human consumption	Research Method patented

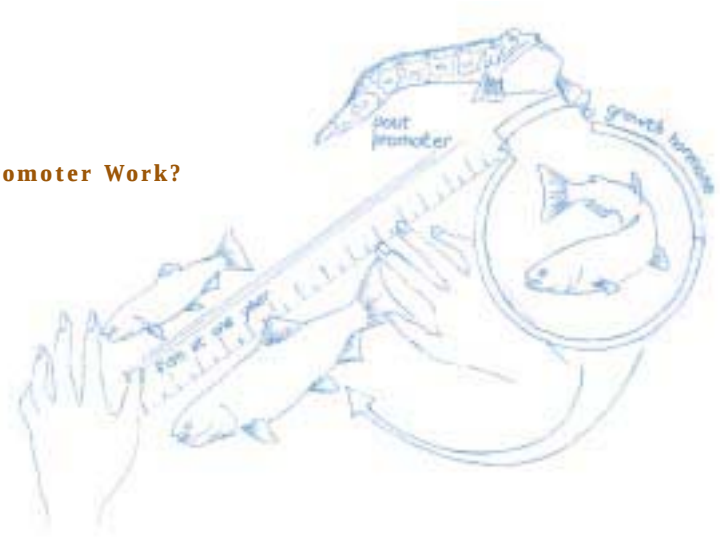
SPECIES GROUP	POTENTIAL BENEFITS	INTENDED END USE OF MODIFIED ORGANISM	PRODUCT STATUS
Marine Plants US patent	Enhanced production of carrageenan or agar (both valuable to the food, pharmaceutical, and cosmetic industries) by seaweed after introduction of foreign DNA.	Industrial application	Research Method patented
Marine Microorganisms US research	Reduced dependence on light for growth in microalgae (diatoms) after insertion of human gene for biochemical involved in metabolism of sugar.	Industrial application	Research
Crustaceans US research	Improved growth rate potential in Kuruma prawns through gene insertion. Researchers are currently inserting marker genes to confirm most appropriate method.	Human consumption	Research

Table 2 illustrates the breadth of transgenic aquatic organisms now in the pipeline, from research through commercialization, and summarizes the potential benefits and intended uses of each. The research and development of transgenic fish focused initially on obtaining huge increases in growth rates—from 2 to 11 times faster than normal—by using growth hormone genes. Scientists have produced faster growing transgenic lines of many fish important to global aquaculture, including both cold water (salmon, trout) and warm water (tilapia, carp) species. A growing number of reports indicate such transgenic fish show better gross food conversion—the increase in fish weight per unit of food fed—than their unmodified relatives (Fu et al. 1998, Fletcher et al. 1999, Cook et al. 2000, Martínez et al. 2000). Fish farmers reap important benefits from more efficient use of food because feeding costs are often the largest portion of total operating expenditures. The environment also benefits from better food conversion because the quantity of fishmeal and resultant waste effluents used to produce a pound of fish decrease. Aquaculture developers are very interested in lowering costs of production through better food conversion, but are equally interested in lowering effluents that require treatment or remediation.

A LOOK AT THE SCIENCE:

HOW TRANSGENIC FISH ARE CREATED

Figure 2: **How Does A Promoter Work?**



In the growth-enhanced transgenic fish produced to date, the inserted genetic constructs typically contain both a growth hormone gene and DNA sequences that control the gene. These DNA control sequences, also known as "promoters," tell the growth hormone gene where and when to turn on and off. The gene may come from either the same fish species as the one being engineered or from a different fish species. However, the key to stimulating dramatically faster growth rates is not changing the growth hormone gene, but rather the "promoter" DNA sequence that controls it (MacLean and Laight 2000). A new promoter can control the production of growth hormone in a manner independent from the fish's traditional system of regulating growth hormones. Selecting the right promoter allows developers to "trick" the fish's cells into making growth hormone when it otherwise wouldn't, so they grow faster or at different times in the fish's development. For example, recently developed transgenic Atlantic salmon owe their rapid growth capability to a DNA promoter from the ocean pout's cold tolerance protein gene (also referred to as an "antifreeze" trait). The ocean pout's promoter tells the genes linked to it to stay "on" in cold temperatures—a factor critical to the ocean pout's ability to survive in its arctic habitat. Unmodified Atlantic salmon normally produce very little growth hormone in colder temperatures. Putting the salmon's growth hormone gene under the control of the ocean pout's cold tolerance promoter, however, causes the salmon to make growth hormone year-round and to reach market size in half the normal time (Hew et al. 1995, Fletcher et al. 1996).

Table 2 also shows that aquatic biotechnologists have quickly broadened their efforts to encompass modification of freshwater and marine plants and shellfish. They have expanded the variety of genes inserted to express a growing diversity of traits. Since disease is a major cause of losses of fish stock, particularly in high-density aquaculture operations, recent aquatic biotechnology research has focused on improving the disease or parasite resistance of fish, mollusks, crustaceans, and other organisms. Table 2 includes an example of improving general disease resistance by inserting a human gene for interferon, a biochemical that strengthens immunity against invading pathogens, into grass carp, a major aquaculture species in China and other parts of Asia. The table also shows that, in the future, scientists may engineer algae, clams, oysters, and fish to act as biological factories that produce industrial chemicals and human or animal pharmaceuticals (see Figure 3). Engineering may also produce transgenic aquatic organisms that thrive in different environments, such as low light for algae or cold water for fish.

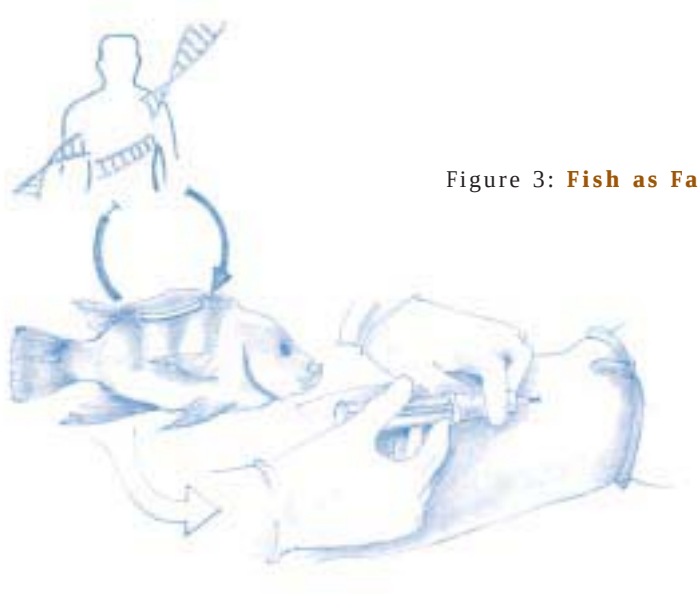


Figure 3: **Fish as Factories**

WHAT IT COULD MEAN:

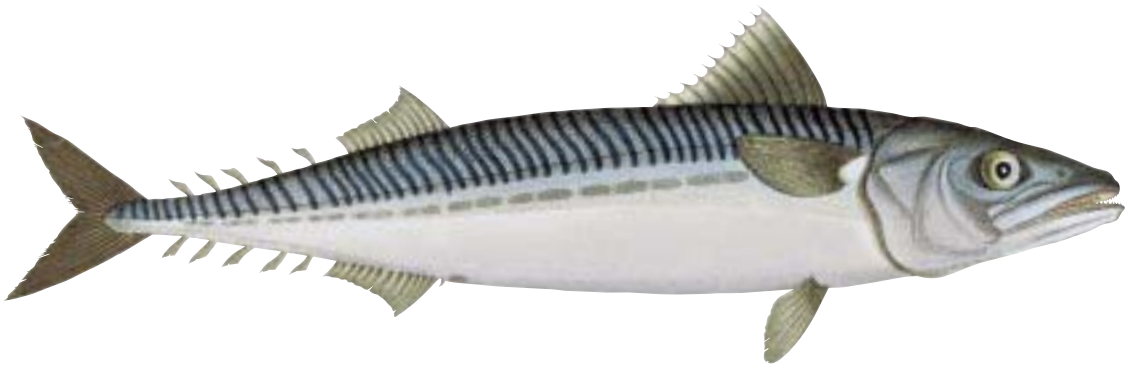
POSSIBLE ECONOMIC IMPLICATIONS

Using biotechnology to dramatically increase the growth rates of salmon and other fish is likely to reduce production costs per unit of food produced and thereby possibly reduce costs to consumers. Lower production costs stem in part from greater efficiency: facilities using net pens can double yields and gross revenue in each growing season if they halve the time needed for a fish to grow to market size. This, in turn, doubles the potential production capacity at each commercial site where fish are grown. In addition, aquaculture operations may be able to reduce input costs. Evidence suggests that faster-growing transgenic species convert food more efficiently, meaning developers can reduce the cost of feed per unit of food produced (Fletcher et al. 1999, Cook et al. 2000). In addition, introducing disease-resistance traits to fish may enable developers to reduce the costs associated with using antibiotics as well as the costs incurred from fish losses due to disease.

While gene transfer technology is likely to increase production efficiency, it is difficult to predict whether any individual firms or market segments will enjoy greater profitability as a result. Whether any given firm will find the technology profitable will depend on a large number of factors. Global supply and demand set prices for fish; if producers rapidly adopt the technology around the world, supply could outstrip demand and prices would fall. But consumer acceptance of genetically modified seafood remains untested. Firms may also face higher costs: in addition to paying a royalty for transgenic eggs, facilities may face higher environmental compliance costs as a consequence of more intense production and, possibly, required confinements for transgenic fish. Actual production efficiencies will likely vary from species to species and from location to location.

As with most introductions of new technologies, some firms and market segments will benefit while others will face adverse affects. The economic impacts on operations of different sizes may vary. For example, if widespread adoption leads to lower prices, smaller facilities might face a competitive disadvantage. Aquaculture competitors—such as commercial fishermen in Alaska whose king, silver, and sockeye salmon compete in the global market with farmed salmon—could face declining profit margins if prices fall. Consumers, on the other hand, would benefit from lower prices.

A more sophisticated economic analysis, which is beyond the scope of this report, would need to take these and other factors into account to predict the impact of the technology on the aquaculture and fishing industries.



chapter

TWO

Environmental Issues

chapter 2

ENVIRONMENTAL ISSUES

INTRODUCTION: A CONVENTIONAL AQUACULTURE AND TRANSGENIC FISH

Conventional aquaculture practices raise a number of environmental issues, including

- water pollution from aquaculture operations;
- possible effects on over-stressed wild fisheries;
- reduced fitness and diminished genetic diversity of wild fish populations by inter breeding with escaped farmed fish; and
- disruptions to wild fish populations and fish communities if escaped farmed fish become established as invasive species that compete for scarce habitat and food.

The application of genetic engineering to aquaculture adds significant new dimensions to these existing issues.

Conventional Aquaculture. Aquaculture systems vary widely for different species and levels of production intensity. Salmon and trout aquaculture, for instance, uses two methods: land-based tanks or open-water pens (see Figures 4 and 5). Each method poses unique environmental challenges. Like other concentrated feeding operations, aquaculture systems can produce large quantities of wastes, bacteria, and chemicals. This is a particular issue for developers using open-water pens because the porous netting used to hold the fish allows pollutants to release directly into natural waters.

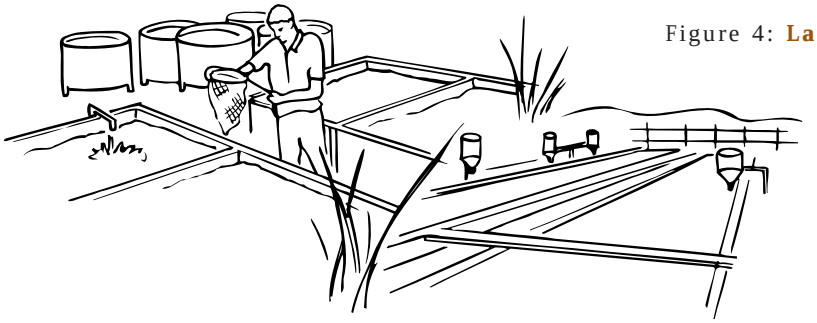


Figure 4: **Land-based Tanks**

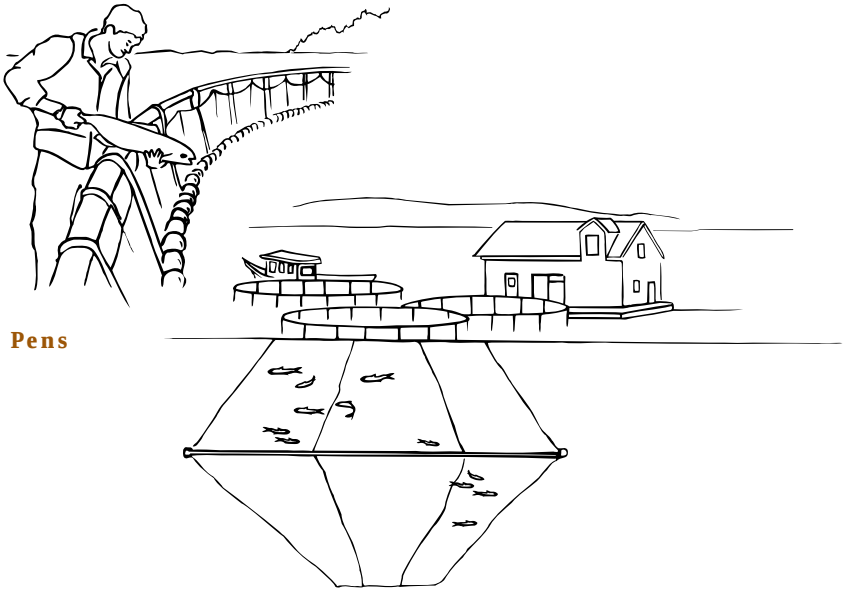


Figure 5: **Open-water Pens**

Nutrient wastes released from open-water aquaculture sites in the form of unused food, feces, urine, and dead fish also raise environmental concerns. Excessive nutrients such as nitrogen and phosphorus, for example, can cause algal blooms, oxygen depletion, and lead to the deterioration of a native fish population. High volumes of organic matter (such as nutrient wastes) can cause water at the sea floor to become *anoxic* (meaning it has little or no dissolved oxygen) and lead to so-called "dead zones" in localized areas directly below the sites. Although aquaculture operations account for a relatively small portion of the total nutrient discharges into the environment, many aquaculture sites are in sensitive areas such as the Gulf of Mexico and the Chesapeake Bay, making their potential environmental impacts that much more controversial (Goldburg, 2001).

The production conditions inherent to aquaculture can also have environmental implications. Commercially produced fish are raised in high-density environments making them more susceptible to diseases such as sea lice and infectious salmon anemia (ISA). To curb the spread of certain diseases and parasites, producers often administer antibiotics through the water, usually as part of the fish feed. On occasion, producers will also apply pesticides. Although producers tend to apply both of these additives in low doses, concern exists that routine use of antibiotics could lead to resistance in pathogens. Some have argued that if fish develop resistance, it could make it more difficult to control diseases in commercial aquaculture operations. Farmed fish that escape could expose wild fish to disease(s) more common to the farmed fish population. The difficulty in controlling diseases could also possibly lead to the presence of antibiotic-resistant pathogens in the environment and in seafood consumed by humans (Goldburg, 2001).

Biotechnology and Aquaculture. The application of biotechnology to conventional aquaculture practices could affect pollution generated by aquaculture operations. Studies indicate that some faster-growing transgenic fish convert food more efficiently than conventional aquaculture stock, suggesting that the amount of wastes relative to the amount of fish produced could be reduced. However, whether the introduction of biotechnology would result in a net reduction or an increase in the total amount of wastes produced would depend on the level of transgenic fish production, which will be largely determined by the economic factors discussed earlier.

Efforts to engineer fish to better resist disease could lead fish farm producers to reduce their use of pesticides and antibiotics. As a result, concerns about pollution, antibiotic resistance, and the risks to human health from higher pathogen levels in seafood could be addressed. The degree to which these concerns would be reduced, however, is difficult to determine and would depend on a number of mitigating factors including the diseases fish could be engineered to resist.

Increased efficiency of aquaculture production could also potentially make it more economically feasible for developers to switch from net pens to more environmentally friendly land-based recirculating systems. Land-based systems tend to have higher operational and capital costs than net pens, but prevent the escape of fish and minimize the problem of discharging wastes into open waters. These systems purify water using biological filters before recirculating it to fish tanks, and generate an organic sludge waste, an environmentally sound crop fertilizer. The likelihood of such a transition to a land-based system depends on a host of market factors that are difficult to predict.

C IMPACTS ON FISHERIES

Manufactured feeds for salmon farming include two important ingredients: fishmeal and oils from the capture fishing of small, wild species not normally used for human consumption. This dependence of aquaculture feed on wild fish has raised concerns that aquaculture might fail to yield a net gain of fish protein for the world (Naylor et al. 2000). However, improved feed conversion of transgenic fish would decrease the amount of fishmeal and oil required for each pound of weight gain, thus decreasing dependence on wild fish per unit weight of harvested-farmed fish. As with the pollution issue, whether this greater efficiency translates into a net reduction or an increase in the use of wild fish needed for fishmeal will depend on the total production of transgenic fish, which will be determined by economic factors. In addition, if there is a significant increase in fish production through the widespread adoption of biotechnology, the increased demand for fishmeal could trigger rising fishmeal prices that could help accelerate efforts to reduce fishmeal use or to find substitutes.

D GENE FLOW:

IMPACTS ON GENETIC DIVERSITY AND HEALTH OF WILD FISH

a. Conventional and Transgenic Aquaculture Fish

The escape of commercially produced fish from open-water pens into surrounding waters presents another potential environmental impact of aquaculture. Producers often breed commercial aquaculture fish through conventional (non-transgenic) techniques for traits that make them more desirable, and thus genetically distinct from their wild counterparts. If the farmed fish escape and mate with sexually compatible wild fish, those genetic differences—and their associated trait—can be introduced into the genes of the wild fish population. The heterogeneity of the wild population can be reduced and biodiversity lost as the unique genetic qualities bred into farmed fish flow into the wild population (Kapuscinski and Brister 2001).

Whether or not escaped farm fish pass their genetic differences on to their wild counterparts will depend on how those genetic differences affect the "net fitness" of the farmed fish—i.e., the likelihood that the farmed fish will survive and reproduce. The environmental consequences of such gene flow, if it occurs, could be benign, or negative, depending upon a variety of factors. Both transgenic fish and non-transgenic fish farmed for commercial purposes could escape from open-water pens and mate with wild fish. However, genetic engineering greatly expands the range of potential traits that scientists can introduce into a fish breed. Some of those traits may decrease the net fitness of a fish, making it less likely to survive and pass its genes to future generations. Other introduced genes may greatly improve net fitness and increase the impact the genetically modified fish could have on wild fish populations. Further, because those genes were not present previously in a fish population in a particular ecosystem, it is difficult to predict how those genetic changes will alter fish behavior or disrupt the ecosystem processes.

In assessing the potential of these risks, a number of factors need to be considered: the potential of escape, the possibility of gene flow to wild related fish populations, and the availability of risk management measures to reduce those risks. The following section discusses the present scientific understanding of these risks and their possible consequences.

b. Escape

Fish cages, traditionally suspended in open water, carry a high risk of escape. Ordinary wear and tear on the equipment, as well as cage damage from storms or predators has reportedly allowed thousands (possibly hundreds of thousands) of farmed fish to escape (Hallerman et al. 1992). Increasing evidence shows that escapees eventually enter rivers to spawn (Carr et al. 1997, Youngson et al. 1997, Gross 1998, Fisk and Lund 1999, Noakes et al. 2000, Volpe 2000, Volpe et al. 2000, Gross 2001). This may cause genes from farmed fish (many of which were conventionally bred to possess certain qualities) to flow to wild, unaltered relatives.

When transgenic fish are involved, concerns about escape vary, depending on case-by-case factors including the number of fish that escape, their genetic composition and fitness, the accessible ecosystems they enter, and the fish populations already in those ecosystems (Agricultural Biotechnology Research Advisory Committee 1995). While improvements to reduce escape can certainly be made, experience suggests that a significant number of transgenic fish will escape from fish pens into open waters. To reduce the impact of escapees, some suggest that state or federal authorities require transgenic fish grown in net pens to be sterile, reducing the ability of transgenic fish to pass on their transgenes to wild relatives. This possibility is discussed in more detail in coming pages.

c. Examining Gene Flow – Net Fitness Parameters

One way researchers attempt to determine if a novel gene will flow to other populations is by assessing the "net fitness" of a particular type of fish. The term *net fitness* is scientific shorthand for the degree to which an organism succeeds at surviving and passing on its genes to future generations. The net effect of the following six traits fully determine the net fitness for any animal, including a transgenic fish (Muir and Howard 2001a):

- juvenile viability (chances of surviving to sexual maturity);
- adult viability (chances of surviving to procreate);
- fecundity (number of eggs produced by a female);
- fertility (percent of eggs successfully fertilized by male sperm);
- mating success (success at securing mates); and
- age at sexual maturity.

Scientists have long considered these as independent or associated factors. Now, scientists use mathematical models to combine these net fitness parameters to assess the potential for an organism—such as a transgenic fish that has escaped into a wild population—to either proliferate or die off. Although these models are not "fool-proof" and can not absolutely predict the outcome of a biologic process, we reference them because they provide an analytic structure for our discussion about genetics and the risk of gene flow.

The net fitness methodology provides a comprehensive and cost-effective way to estimate the probability of gene flow and identify the most likely gene flow scenario. It requires first gathering data on the six fitness traits of both transgenic and wild fish in contained experiments and then entering the data into a computer simulation model. So far, researchers have only published complete estimates of net fitness for a transgenic line of a tropical fish species known as Japanese medaka, or rice fish. This species' short generation time (approximately two months) makes it a practical model for risk assessment research. However, few known studies are underway presently to measure the six fitness traits of transgenic fish lines intended for commercial use.

d. Gene Flow – the "Purge" Scenario

Depending on the interaction among the six fitness components, the risk of gene flow can range from none to significant. When the net fitness of a transgenic fish is lower than that of its wild relatives, natural selection will quickly purge any transgenes inherited by wild relatives. It is realistic to expect certain lines of transgenic fish, but not all, will fit this Purge scenario (see Figure 6). Recent research shows that some transgenic lines of growth-enhanced fish will likely have very low net fitness, meeting the Purge scenario (Muir and Howard 2001). It is important to note, however, that the Purge scenario is not necessarily "impact-free." Although, under this scenario, genes of the transgenic fish would ultimately disappear from the native fish gene pool, the disruption of the gene pool during that period could have longer lasting, subtle effects on the population. In a small population, even temporary declines in fitness could threaten the population's survival.

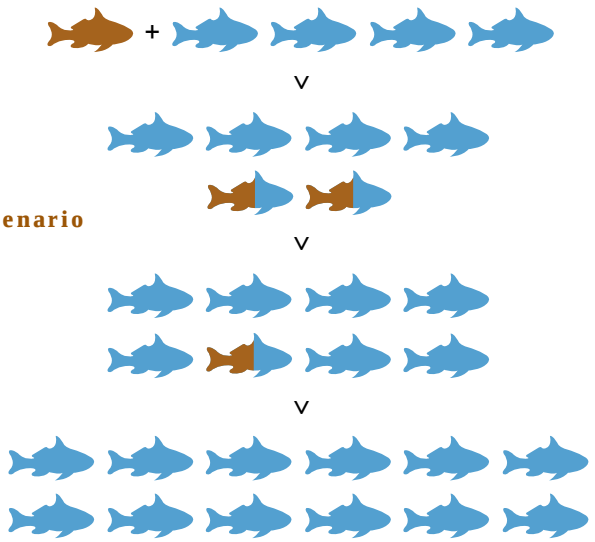


Figure 6: **Purge Scenario**

fish carrying "wild" or "native" genes

fish carrying transgenic DNA

> *movement from one generation to the next and the related gene flow*

The actual number of fish per generation and the number of generations needed for any scenario to unfold varies case by case; thus the numbers shown in these figures are purely illustrative and may not reflect any real case.

e. Gene Flow – the "Spread" Scenario

When the net fitness of a transgenic fish is equal to or higher than the net fitness of a wild mate, gene flow is likely to occur and the genes of the transgenic fish will spread through the wild population (see Figure 7). Recent studies suggest that age at sexual maturity has the greatest effect on net fitness in this Spread scenario, followed by juvenile viability, mating advantage, female fecundity, and male fertility (Muir and Howard 2001, Rodriguez-Clark and Rodriguez 2001). Some publicly available data consistent with a Spread scenario (described in the following pages) were collected from studies of fast-growing transgenic coho salmon containing novel growth hormone genes. These fish reached sexual maturity earlier in life than their wild counterparts (Devlin et al. 1994), as did one transgenic line of fast-growing medaka (Muir and Howard 2001). Additionally, one transgenic line of faster-growing rainbow trout (Devlin et al. 2001) and tilapia (Rahman and Maclean 1999) reached sexual maturity sooner than unmodified counterparts.

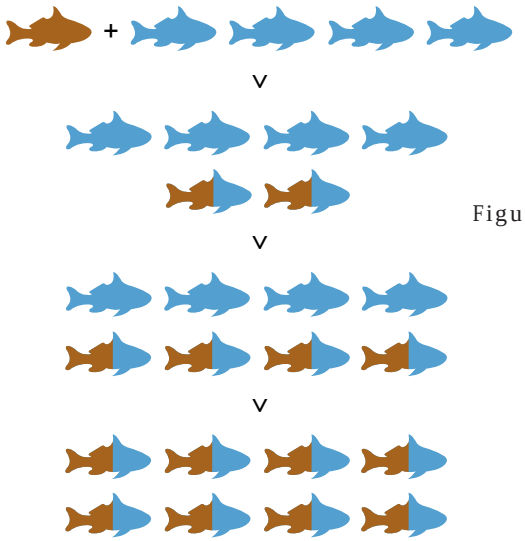


Figure 7: **Spread Scenario**

fish carrying "wild" or "native" genes

fish carrying transgenic DNA

> *movement from one generation to the next and the related gene flow*

The actual number of fish per generation and the number of generations needed for any scenario to unfold varies case by case; thus the numbers shown in these figures are purely illustrative and may not reflect any real case.

f. Gene Flow - the "Trojan Gene" Scenario

A recently developed model indicates the possibility of a third outcome—the Trojan Gene scenario (see Figure 8). The model suggests that an introduction of transgenic fish with enhanced mating success, but reduced adult viability, into a wild population could result in a rapid decline of the wild population. Essentially, the mating advantage would drive the transgene into the wild population, rapidly spreading novel genes. The lower survival of each consecutive generation carrying the transgenes, however, would eat away at the population size (Muir and Howard 1999, 2001, 2001b). An alternative form of this Trojan Gene scenario is possible if the transgene increases juvenile viability—as might occur in fish engineered to contain a new disease resistance gene—but at the same time reduces fertility (Rahman and Maclean 1999). Interbreeding between such transgenic fish and the wild population could trigger a dramatic population decline.

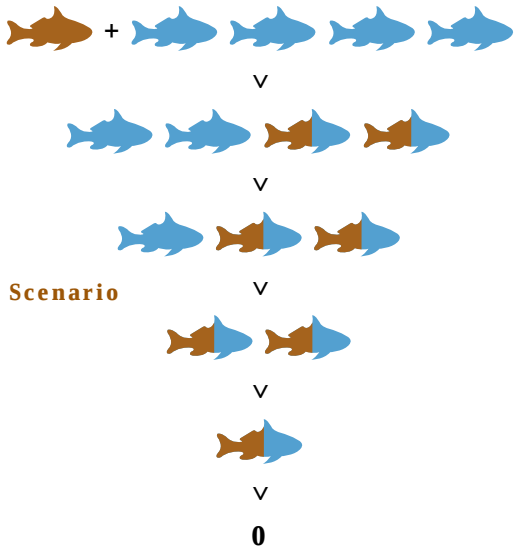


Figure 8: **Trojan Gene Scenario**

fish carrying "wild" or "native" genes

fish carrying transgenic DNA

> *movement from one generation to the next and the related gene flow*

The actual number of generations needed for any scenario to unfold varies case by case; thus the numbers shown in these figures are purely illustrative and may not reflect any real case.

It is important to note the difficulty of predicting whether a Trojan Gene scenario could occur. Scientists currently lack the empirical information needed to assess whether, and when, strong natural selection could emerge and counteract the Trojan Gene effect.

g. Gene Flow – Potential Environmental Consequences

If novel genes do spread into wild populations, the possible environmental consequences are extensive, but remain difficult to determine. The most important consequences vary case by case, depending on the most likely gene flow scenario, and the ecological characteristics of the transgenic fish and the fish community it might affect (Scientists' Working Group on Biosafety 1998, Letourneau and Burrows 2001).

All of the aforementioned scenarios could have consequences for wild fish populations, such as commercially significant, threatened, or endangered species. They could also have consequences for the wider aquatic communities in which the wild populations may play an important ecological role, as well as an impact on the resilience of those communities. Fish communities (the interconnected groups of fish species and other aquatic organisms living in the same environment) have a level of resilience that enables them to recover from shocks caused by either nature (e.g., hurricanes) or humans (e.g., toxic waste spills) and then return to a state resembling a pre-shock condition. In contrast, a community that has lost resilience responds to major shocks by shifting, often rapidly and with only subtle warning, into an unstable and degraded state characterized by dramatic loss of biodiversity, for example, or sudden over-dominance by a nuisance species.

Major gaps exist in the scientific understanding about what interactions among different aquatic organisms—and between organisms and their environment—drive the resilience of a fish community. The difficulty in prediction increases with the degree of novelty of the transgenic fish's traits compared to wild fish in the community. Reductions in fish community resilience may be irreversible or difficult and expensive to undo.

Of all the scenarios discussed, however, the Trojan Gene scenario clearly poses the most obvious concern because it could cause decline of the wild fish population into which the gene is introduced. The loss of a population could result in loss of unique genes, closing off options for future breeding and biotechnology programs that harness unique genes to improve aquaculture broodstocks. These losses might also harm any diminished wild population's ability to rebuild its numbers and persist over the long term. If the Trojan Genes are passed on to a threatened or endangered species, the added influence could greatly increase that species' risk of extinction. A declining fish population would also have secondary impacts on other aquatic species that feed on, or otherwise depend on it. Populations unable to successfully switch to another food source, or those whose survival or reproduction depends directly on the declining population, would also suffer.

The consequences of the Spread scenario is more complex, in part because the impacts are more subtle and will vary depending on many factors, including the specific genetic trait involved. While wild fish may not suffer declines at the population level, changes in their genetic makeup caused by gene flow can lead to changes with ecosystem-wide impacts. Empirical data, population genetics theory, and some models predict that differences between the genetic makeup of the transgenic fish line and the wild fish population could gradually disappear, creating one homogenized genetic resource (Kapuscinski and Jacobson 1987, Busack and Currens 1995, Meffe and Carroll 1997). In other words, the unique genetic make-up of the wild fish population would no longer exist as it had, due to the interbreeding with the escaped transgenic fish.

This homogenization of the gene pool can have many consequences. On the negative side, the gene pool could lose rare alleles (alternative versions of a given gene), jeopardizing the future availability of unique wild genes that might be needed in the future to combat diseases or improve other traits of aquaculture broodstocks. In some cases, the total genetic diversity of a wild species population could decrease. The loss of genetic diversity would also jeopardize the ability of wild fish populations to adapt to changing environmental conditions and, thus, to persist over the long term. These consequences would be most severe in "centers of origin," those special geographic regions where a species originates, eroding the genetic insurance policy provided by these regions and undermining the stability of healthy wild populations.

Effects on the fish community and ecosystem as a whole are more difficult to assess. The "homogenized" genetic pool that could result from the Spread scenario could produce a healthy and stable fish population. However, the unique genetic make-up of the original wild fish population would have been altered, and many conservationists would argue that the loss of biodiversity is itself a negative impact (for reasons previously cited).

While it is likely that the spread of novel transgenes into a wild fish population will have impacts, given the limitations of current science, it is extremely difficult to predict and assess the consequences of those impacts on fish populations and the broader aquatic communities to which those populations belong.

Another fundamental issue associated with escapes of transgenic fish is their potential to become an invasive, "exotic" species in an ecosystem lacking wild relatives. Invasion of aquatic environments by any exotic species, whether transgenic or not, raises concerns about potential environmental harm. The following discussion refers specifically to transgenic fish that, although retaining most of the traits of their unmodified parental species, exhibit one or more novel qualities that give them an ecological advantage.

While any introduced species can become a nuisance species, traits introduced by genetic engineering can affect the probability of a species becoming established and invasive. One example is the transfer of "antifreeze" protein genes into goldfish, resulting in increased cold tolerance (Wang et al. 1995, CEQ-OSTP 2001). Large-scale production of such goldfish could raise the possibility that this exotic species, already established in some U.S. inland waters, would greatly increase the range it invades and, through its prolific breeding and hardy nature, becomes a nuisance.

The large-scale engineering of species already recognized as a pest or nuisance might raise the greatest concern about genetically modified fish. For example, scientists could intentionally engineer a member of a pest species, such as sea lamprey or zebra mussels, to spread a debilitating gene to a thriving, unmodified population once released into the wild. Although such an act could be a successful biological control, it would be critically important to consider evolutionary and ecological processes that might backfire on the biological control's objective.

a. Establishment of an Invasive Species

When assessing the potential of a transgenic fish to become an invasive species, one consideration is a comparison with the invasive potential of its unmodified "parent." Escaped transgenic fish could quickly disappear from the environment if their invasive ability, as a direct or indirect effect of their engineered genes, is severely reduced compared to their unmodified counterparts. One indicator is if their net fitness is much lower than that of the non-transgenic counterpart. This is the most benign environmental scenario, although the transgenic fish would have to disappear quickly to avoid causing lasting harm to other species in the ecosystem.

On the other hand, a fit and fertile transgenic fish would be more likely than its non-transgenic counterpart to establish a self-sustaining exotic species population in the accessible ecosystem if its engineered genes conferred greater invasive ability (NRC 2002). The functional equivalent of this scenario, sometimes called the Establishment Scenario, may also occur if most invading transgenic fish are sterile, but enter the ecosystem in recurring waves of large numbers, with each wave replacing the earlier one as it dies off (Kapuscinski and Brister 2001). This could occur through escapes from unsecured aquaculture operations or intentional fish stocking programs.

b. Consequences of Exotic Species Invasion

If transgenic fish become established, they may compete with or prey on threatened, endangered, or beneficial species in the invaded ecosystem, leading to either a decline in the affected species or to a co-existence between the two. The most severe consequence would be an accelerated decline in the abundance of an already threatened or endangered species, triggered by superior competitive ability or superior predation of the invading transgenic fish.

If the established transgenic fish show increased competitive ability or predation success, a change in the abundance of at least one other species in the ecosystem is inevitable (Scientists' Working Group on Biosafety 1998). Whether or not this significantly reduces community resilience would depend on the number of species affected, the role of the affected species in the overall food web, and the magnitude of change in their abundance. For many accessible ecosystems in U.S. waters, information needed to consider such factors is inadequate or nonexistent.

Unfortunately, assessing the likelihood of invasion by transgenic fish (and, by extension, its possible environmental consequences) is difficult because so little is known about the likelihood of invasion by unmodified aquatic species. Although a large body of scientific information on invasive species exists, most of it is based on evidence collected *after* invasions that caused major environmental and economic changes (Riedmiller 1994, Goldschmidt 1996, Gido and Brown 1999, Williams and Meffe 2000). Retrospective analyses of large databases have yielded some rules of thumb:

- roughly 3 percent of cases where fish are introduced to a new environment result in invasion; and
- 2-3 percent of established invasive species can spread further and expand their range (Williams and Meffe 2000).

However, predicting invasion success and consequences *before the fact* remains very difficult (Di Castri 1999, Moyle and Light 1996, Parker et al. 1999).

RISK MITIGATION: USE OF STERILE FISH TO REDUCE RISKS OF GENE FLOW AND EXOTIC SPECIES INVASION

To reduce ecological risks associated with unintentional releases, some scientists have recommended applying a mix of biological and physical containment measures to transgenic aquatic organisms. The strategy most often discussed, and the one already used in some aquaculture operations, is sterilizing farmed fish. The present approach to sterility, called "induced triploidy," involves manipulating newly fertilized embryos to have an extra pair of chromosomes by applying a temperature, pressure, or chemical shock. These triploid fish are sterile, but otherwise normal. Methods to induce sterility are relatively easy and inexpensive, and have already been applied to some aquaculture species, such as rainbow trout, Atlantic salmon, and oysters. There are, however, drawbacks to relying solely on induced sterility to prevent the environmental hazards posed by transgenic fish (Agricultural Biotechnology Research Advisory Committee 1995).

First, the effectiveness of triploidy induction varies greatly, depending on species, methods used, and egg quality. Success rates range from 10 to 95 percent (Maclean and Laight 2001). One screening method removes those fish that failed to become triploid before their transfer from secure hatcheries to much less secure growth facilities such as open-water cages (Kapuscinski 2001). Unfortunately, this method requires checking every individual fish manually. Presumably, however, most developers of transgenic fish will want to market fertilized eggs, and one cannot screen fertilized eggs with this method. Some have suggested checking samples from groups of fish to see if individuals are triploid, but this introduces the possibility that some untested fertile individuals may accidentally be certified as sterile.

Even if sterility could be assured, release of triploid fish into the environment presents certain hazards. Triploids of some species, while sterile, still have enough sex hormones in their bloodstream to enter into normal courtship and spawning behavior. Escaped sterile triploid fish could interfere with the reproduction of wild relatives by mating

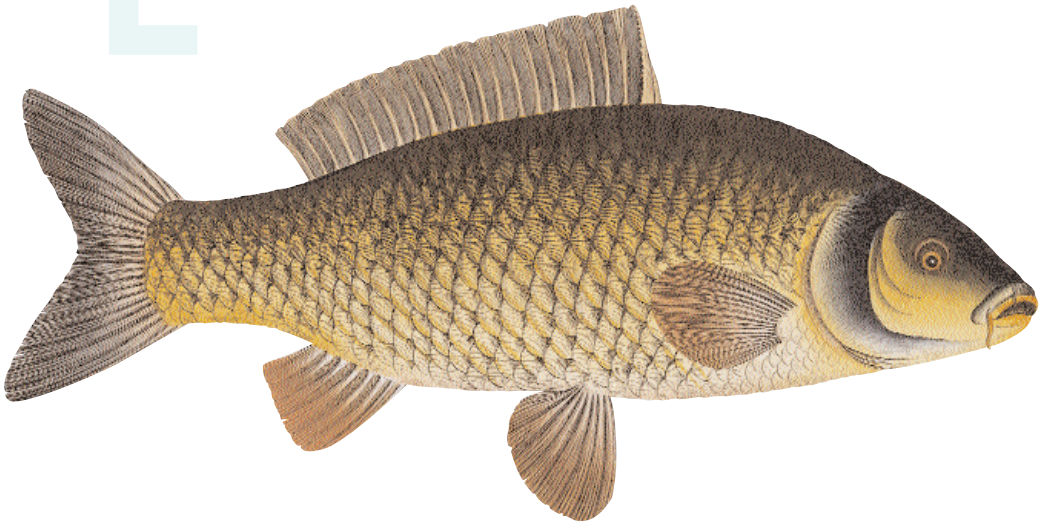
with fertile wild adults. The most severe consequence would be reproductive interference of declining, threatened, or endangered species. In trout and salmon, the concern appears mostly with triploid males, according to some studies (Inada and Taniguchi 1991, Kitamura et al. 1991, Cotter et al. 2000). In these cases, making the transgenic fish all-female, in addition to making them sterile, may reduce the concern (Donaldson and Devlin 1996).

Finally, some sterile fish survive and grow beyond their normal lifespan, perhaps because they do not expend energy on reproduction or enter senescence like fertile fish. In cases where large numbers of such transgenic fish enter the environment on a recurring basis, they might pose heightened competition with wild relatives or contribute to higher predation on other species (Kitchell and Hewitt 1987).

chapter

THREE

Food Safety Issues



chapter 3

FOOD SAFETY ISSUES

Fish are an important staple of the human diet. Therefore, an analysis of transgenic fish must consider the possible risks (and benefits) presented if such fish were to enter our food supply. This section provides an overview of several human health issues, including some interesting (albeit speculative) advantages, which could be presented by the introduction of transgenic fish. This discusion pays particular attention to the possibility that risks inherent to current fish populations (i.e., toxic compounds, allergens, and hormones) may be more complex in transgenic aquaculture.

A TOXIC COMPOUNDS

Some fish contain toxins that make their tissue dangerous for humans to consume—especially if those compounds reach particularly high levels. Some toxins, such as mercury, found in several commonly consumed fish and shellfish, are absorbed from the environment (EPA 2002). Scientists are concerned that gene transfer could inadvertently cause tolerance in a transgenic fish to the toxin, thus allowing higher levels to accumulate in their tissues. This, in turn, could pose a danger to humans and other animals eating the tissue of that fish (National Wildlife Federation 2002). Other toxins, such as tetrodotoxin found in some species of puffer fish, are sequestered by the fish from the food they consume (U.K. HGMP Resource Centre 2002). There is some concern that genetic engineering could cause fish to sequester higher levels of this toxin, due to indirect effects in the transgene on the uptake, retention, and metabolism of such poisons (Kapuscinski and Hallerman 1994).

Another noteworthy concern is that gene transfer could cause a transgenic fish or shellfish to produce a novel toxin and make the fish's tissue dangerous for humans or other prey to consume. It is important, therefore, to carefully screen transgenic fish and shellfish for unintended increases in accumulated toxins due to indirect effects of the transgene on the uptake, retention, and metabolism of these compounds. Some scientists, however, argue that transgenic fish and shellfish are generally unlikely to produce novel toxins unless explicitly engineered with genes for toxic proteins (Berkowitz and Krypsin-Sorensen 1994).

B ALLERGENS

Many people are allergic to fish and other aquatic organisms. Although research on food allergies is limited, scientists do know that allergic reactions are responses to proteins in a select food and that different people may be allergic to different parts of a protein. Some aquatic organisms, such as crustaceans, mollusks, and certain fish, trigger moderate to severe allergic reactions in susceptible individuals. Knowledge is incomplete about which protein (or portion of proteins) cause people to react.

It is possible that the process of genetically engineering aquatic organisms could accidentally increase the allergic potential of that organism. The gene introduced could cause the fish to produce a protein it previously had not produced, or change the composition of a protein such that it now triggers the allergic reaction. Researchers could also use a gene from an organism people traditionally do not eat and for which allergic potential is unknown. Each of these outcomes could increase the number of people who experience food allergies or alter the severity of allergic reactions to seafood (Kapuscincki and Hallerman 1994).

C HORMONES

Plants and animals produce many different hormones, each playing a distinct role in regulating an organism's physiology. Most hormones do not act independently, but rather affect and are affected by, a number of others. In fish, for example, an increase in growth hormone raises the levels of other growth promoters (Moriyama 1995). Hormones secreted by other vertebrate animals, such as fish, tend to be biologically inactive in humans because they do not sufficiently resemble the human version of the hormones that bind with growth hormone receptors on human cells. For example, the Food and Drug Administration (FDA) evaluated this issue in the late 1980s, finding no increased health risk to consumers from the use of recombinant bovine growth hormone (rbGH) in dairy cattle.

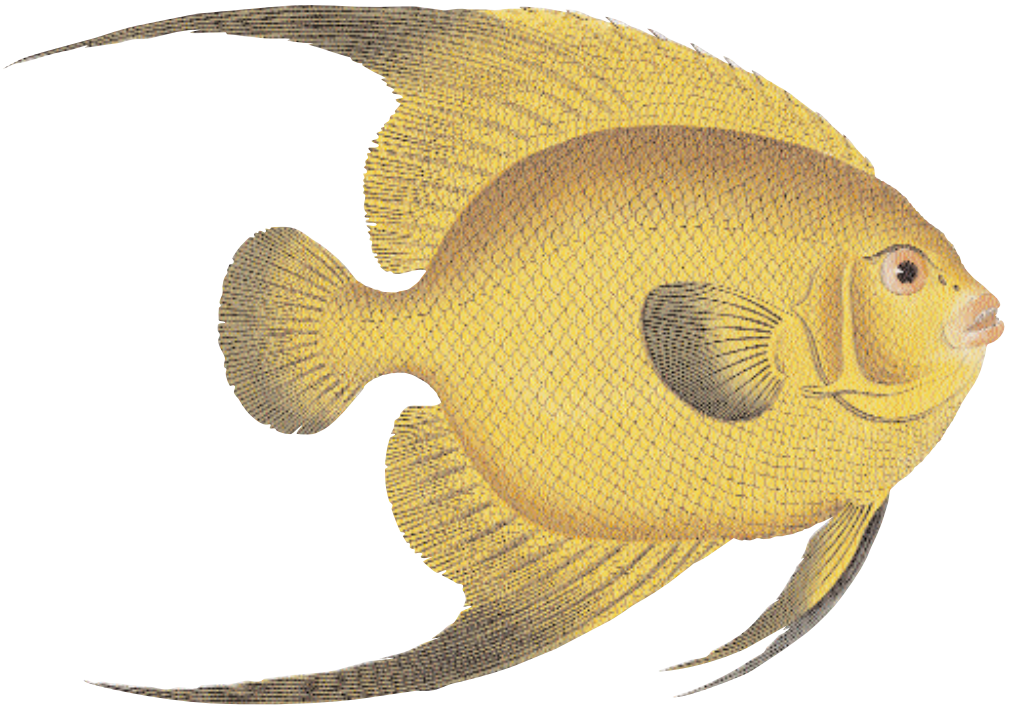
Testing methods to determine how and where growth hormones (and other compounds) accumulate in fish tissues are fairly well established. Although the act of cooking fish renders harmless any growth hormone residues that might exist, raw fish flesh, such as sushi, could retain biologically active hormone residues (Kapuscinski and Hallerman 1994).

D POSSIBLE FUTURE ADVANTAGES

Although much has been written about the risks thought to be associated with transgenic aquaculture, it is important to note the potential it offers researchers in addressing some important food safety and environmental concerns.

For instance, what if biotechnology could be used to *reduce* the amount of mercury or other toxic compounds that some fish accumulate from their environment? The same line of thinking could also be applied to concerns about allergies. What if researchers could identify and remove the various proteins that make shellfish intolerable for some consumers and produce a line of shrimp or crab those individuals could consume? In fact, scientists at Tulane University have already identified the major allergens in shrimp that cause allergic reactions in some people, and begun to use genetic engineering to alter proteins so shrimp no longer induce such reactions. Genetic engineering could also have significant advantages for the environment. What if scientists could develop a transgenic fish able to detect pollutants or mutagens in the aquatic environment, becoming darker upon exposure and alerting humans to water quality problems? Some researchers in Singapore are looking at using transgenic zebra fish for this purpose. These scenarios, on the brink of becoming realities, and others that have yet to be conceived, make readily apparent the potential benefits of applying biotechnology to aquaculture.

As regulators, policymakers, and the public consider the many issues presented by transgenic fish, they must be careful not to obscure benefits not readily apparent in the first generation of products, but may emerge once the technology has had a chance to proliferate.



chapter

FOUR

Regulation

chapter 4

REGULATION

OVERVIEW

Since the mid-1980s, when the first genetically modified products began moving from the lab toward commercialization, federal policy has regulated biotechnology products no differently than similar products produced in a conventional manner. As a result, the regulation of biotechnology products depends on what they are and their intended use. So, for example, genetically modified food crops are reviewed for food safety under the same laws that apply to conventional foods.

When the government first adopted guidelines for biotechnology regulation in 1986, it believed existing statutes would adequately cover all of the biotechnology products then foreseen. Where potential overlaps of legal authority existed, agencies were directed to coordinate policies with each other. For many products, such as transgenic organisms with pesticidal properties, lead agencies were designated (Office of Science and Technology Policy, 1986).

For the most part, existing laws have proven sufficiently flexible to cover the biotechnology products brought to market since that time, though not without controversy. Now, sixteen years later, biotechnology research is poised to bring to market new products that will be more difficult to fit under existing statutes.

Transgenic fish and aquatic organisms are examples of these emerging uses of biotechnology. The 1986 Coordinated Framework for the Regulation of Biotechnology did not specify the lead agency for transgenic fish and other aquatic organisms because scientists had not yet fully developed such applications. Now that at least one variety of transgenic fish is poised to come to market, and others are not far behind, a number of laws appear to have potential application. To date, however, the federal government has not formally announced a unified regulatory framework for fish or other transgenic aquatic organisms. But the regulatory framework ultimately selected will have significant implications for industry, consumers, as well as the environment, and raises a number of important public policy issues. It also illustrates some of the challenges facing regulators as they try to apply existing laws to novel biotechnology products.

As noted in prior sections of this report, transgenic fish and aquatic organisms raise both food safety and environmental concerns. This section of the report reviews several possible alternative sources of legal authority for reviewing the food safety and environmental impacts of transgenic fish, and briefly discusses the respective advantages and disadvantages of each alternative. The report also discusses in more detail the effect of FDA's intention to regulate the genetic modifications of transgenic fish (and other transgenic animals) as "new animal drugs" under the provisions of the Federal Food, Drug, and Cosmetic Act. The question is not so much whether federal laws exist that apply to transgenic fish, but rather, whether any of those laws adequately address the specific food safety and environmental issues associated with transgenic fish in a clear, transparent, and credible manner.

B POTENTIAL LEGAL AUTHORITIES FOR REGULATING TRANSGENIC FISH AND AQUATIC ORGANISMS

a. Food Safety: Potential Legal Authorities

The FDA administers the Federal Food, Drug, and Cosmetic Act (FFDCA; 21 U.S.C. §301 et seq.), the primary food safety law for most foods, including seafood. (The U.S. Department of Agriculture oversees the safety of meat, poultry, and dairy products.) The FFDCA spells out different regulatory approaches for different aspects of food and drugs. This section of the report reviews three different approaches that could potentially apply to transgenic fish:

- regulating transgenic fish as "substantially equivalent" to conventional food;
- regulating transgenic fish as food additives; and
- regulating transgenic fish, and their associated genetic modifications, as new animal drugs.

In general, the Act presumes the safety of food already in the food supply, and thus, new varieties of food do not require the FDA's approval before going to market. In contrast, the Act does not afford food additives and new animal drugs the presumption of safety, and so these cannot be sold until the FDA determines the safety of the additive or the safety and efficacy of the new animal drug. Thus, whether regulators treat transgenic fish as food, or whether they treat the genetic modifications as food additives or new animal drugs, will have a dramatic impact on the approval and marketing of transgenic fish.

Option 1: "Substantial Equivalence" Approach

As stated above, FFDCA presumes the safety of foods that have been a part of the human food supply for many years. The FDA generally considers new food crop varieties, whether bred conventionally or through biotechnology, to be as safe as prior varieties of the same crop.[3] For instance, a new corn variety, which may have been conventionally bred or genetically engineered to be a particular shade of yellow, would be considered

[3] In the area of food crops, the FDA regulates new varieties of crops produced through biotechnology as if they were "substantially equivalent" to their conventional counterparts, unless they have been changed in some material way (Food and Drug Administration 1992). In effect, the FDA argues that such varieties can be presumed to be as safe as their conventional counterparts, which have been part of the human food supply for years. As a result, new crop varieties developed through biotechnology are not subject to a pre-market approval by the FDA. However, the FDA encourages manufacturers to voluntarily consult with the Agency before bringing biotech products to market. The FDA believes that all manufacturers to date have complied with this voluntary consultation process, and the FDA has proposed new regulations that would require manufacturers to notify the FDA before introducing any new genetically modified food (66 Fed. Reg. 4706, January 18, 2001).

"substantially equivalent" to common corn varieties and could be brought to market without any FDA oversight. If a new variety is materially different in some way that could affect animal or human health (such as the inclusion of an unexpected allergen or an increased level of a toxin), then the FDA could require labeling or otherwise take action.

The human diet has included fish and shellfish for many years. A developer therefore is not required to get FDA approval for a new conventionally-bred hybrid fish breed before it can be grown in aquaculture pens and sold commercially. This regulatory approach could theoretically apply to transgenic fish as well. The FDA could choose to treat transgenic fish as "substantially equivalent" to other conventionally bred aquaculture fish, much in the same way it has chosen to regulate genetically modified crops. If the genetic modification results in some increase in toxicity or allergencity, reduction in nutrition, or some other material change, the FDA could require additional approvals. If the FDA were to adopt this regulatory approach, the developer of the transgenic aquatic organism could proceed directly to market without prior FDA review or approval. Since no regulatory proceeding would take place, the FDA would have no opportunity to review scientific data nor would the public have an opportunity to participate in the process. (The FDA could presumably encourage developers to voluntarily consult with the agency before bringing the fish to market, as it has done with crops.) The developer would accept legal responsible for ensuring the safety of the fish or aquatic organism.

Option 2: Food Additive Approach

Some have argued that the genetic constructs added to transgenic fish through biotechnology, as well as the proteins they express, should be considered food additives as defined by the FFDCA (Center for Food Safety, 2002). The FFDCA defines a food additive as "any substance, the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of, or otherwise affecting the characteristics of any food…if such substance is not generally recognized… as safe under the conditions of its intended use" (21 U.S.C §321(s)).

Before a producer can market a food additive, the FDA must approve it as safe, defined by the law to mean a "reasonable certainty of no harm." However, if a substance is "generally recognized as safe" (or "GRAS"), it is not considered an additive and may

enter commercial use without prior FDA approval.[4] In theory, the burden to show a substance as safe lies with the manufacturer. However, if the manufacturer claims the substance is "generally recognized as safe," the burden lies with the FDA to demonstrate otherwise through an enforcement proceeding. The FDA determines the safety of a food additive through a rulemaking process with opportunities for public comment. Once the FDA determines the safety of a food additive, any food manufacturer can use it for the approved purposes.

Option 3: New Animal Drug Approach

Under the FFDCA, the FDA also regulates animal drugs (other than veterinary biologics) to ensure their safety and efficacy. The FDA has asserted that the genetic constructs used to transform genetically engineered fish (and other animals) fall under the FFDCA's definition of a "drug" as including "articles . . . intended to affect the structure or function of the body of man or other animals." The FDA's definition of a "new animal drug" in this context is not limited to the genetic construct alone. The FDA also considers the expression product of the genetic construct, for example a growth hormone, to be a "new animal drug." Finally, because the construct is integrated into the fish's genome and stably inherited by its progeny, subsequent generations are also considered to contain the new animal drug.

An application process conducted by the FDA establishes the safety and efficacy of new animal drugs. During the application process, the developer must demonstrate a reasonable certainty that no harm will come to individuals who use the product under prescribed conditions. The developer must also show that it has sufficiently tested the product to draw such conclusions. Assuming that the FDA is satisfied with the developer's efforts to answer these questions, it will issue a permit, enabling the developer to commercialize the product.

Given the FDA's announced intention to rely on this last option to regulate transgenic fish, a more detailed consideration of the new animal drug application process, as well as some of the policy implications of the FDA's decision, are discussed in greater detail later in this section. Before that discussion, however, it is important to consider the options available for regulating the environmental concerns associated with transgenic fish.

[4] A developer might argue that the genetic construct and expression products of a transgenic fish modified to grow more quickly would be "generally recognized as safe." The FDA has found previously that DNA itself, as a ubiquitous element in our food supply, poses no food safety risks. As noted in the first section, the FDA has also found that growth hormones secreted by fish are biologically inactive in humans. Other genetic modifications, however, such as for disease resistance, are less clear.

b. Environmental Impacts: Regulatory Approaches

As with food safety concerns, however, a number of laws and regulatory approaches could theoretically be used to review or regulate the environmental impacts of transgenic fish. This section briefly reviews three options:

- regulating transgenic fish under existing federal laws that apply to conventional aquaculture;
- regulating transgenic fish or their genetic modifications as a "new chemical substance" under the Toxic Substances Control Act (TSCA); and
- regulating transgenic fish as a "new animal drug" under the FFDCA.

Each approach has strengths and weaknesses, and a detailed examination of each is beyond the scope of this report. The critical point, however, is that each path is very different. Depending on the regulatory path taken, the review will involve different agencies (with differing levels of experience and expertise), different legal standards, different sets of legal tools to manage environmental risks, and very different regulatory processes that will affect the ability of the public to understand or participate in the decision-making process.

Option 1: Conventional Aquaculture Approach

As noted previously, conventional aquaculture raises environmental concerns. While those concerns have traditionally focused on pollution, increasing concern focuses on the impacts of the escape of fertile aquaculture fish on wild fish and fish communities.

One regulatory option is simply to review the environmental impacts of transgenic fish in the same way that environmental impacts of conventional aquaculture are considered. Given the fragmented federal regulatory authority, however, this approach would mean only a limited federal review of environmental impacts prior to commercialization of the fish.

No single federal agency has responsibility for regulating the environmental aspects of aquaculture. Regulatory responsibilities are spread over a number of federal agencies and stem from a number of different laws intended to address a range of issues. (See sidebar, *How Is Aquaculture Regulated?*). The existing federal approach to aquaculture has been criticized for its fragmented nature and for its failure to adequately address environmental risks of aquaculture (Goldburg et al. 2001, Goldburg and Triplett 1997.) No clear federal authority regulates aquaculture operations to prevent impacts on wild fish communities from gene spread or the introduction of an invasive species, unless the wild fish are threatened or endangered under the Endangered Species Act. Broad state authority to regulate fisheries further complicates the regulatory picture.

The most likely federal review of the environmental impacts of transgenic fish on wild fish would come as part of the environmental assessment carried out by the Army Corps of Engineers as part of its permitting process for aquaculture facilities in navigable waters. (See sidebar for details.) While the permit aims primarily to avoid obstructions to navigation, the National Environmental Policy Act (NEPA, 42 U.S.C. §4321 et seq.) generally requires the Corps to conduct an environmental assessment of the proposed project.[5] As part of that assessment, the Corps could consider the impacts of transgenic fish escaping into the environment and becoming an invasive species or adversely affecting related wild fish populations by breeding and spreading their transgenes. However, NEPA does not provide agencies with additional substantive authority for making regulatory decisions. The NEPA assessment requirement is merely procedural and does not require agencies to act on the basis of the assessment. Agencies can also create categorical exclusions from NEPA. As a result, NEPA cannot provide substantive legal authority for the regulation of the environmental impacts of transgenic fish.

[5] Under NEPA, an initial environmental assessment (EA) is used to determine if an in-depth environmental impact statement (EIS) is needed. If required, an EIS examines i) long- and short-term environmental effects posed by the Agency's action, ii) alternative actions that could be taken, and iii) a summary of environmental resources that would be used if the Agency's action occurs. The EIS is often accompanied by comments from other federal agencies with special knowledge of the anticipated environmental impacts.

How Is Aquaculture Regulated?

Regulation of aquaculture occurs on both the state and federal level. States have oversight of resources within their borders and of marine resources up to three-miles from their coasts (Hallerman 2002). It is not surprising, then, that states have passed some of the most decisive legislation to date about transgenic fish. (Legislation in Maryland bans the introduction of genetically modified fish in state waters, and lawmakers in California recently considered (but later rejected) similar legislation.) In comparison, federal regulation is less centralized, as it is administered by several agencies using a variety of statutory and regulatory provisions. This includes the National Marine Fisheries Service (NMFS) of the National Oceanic and Atmospheric Administration (NOAA) at the Department of Commerce, the Environmental Protection Agency (EPA), the Army Corps of Engineers (ACOE), the Fish and Wildlife Service (FWS) at the Department of the Interior (DOI), and the U.S. Department of Agriculture (USDA).

Federal laws applying or relating to the environmental implications of aquaculture include, but are not limited to, the Clean Water Act (31 U.S.C. §1251 et seq.), the Rivers and Harbors Act (33 U.S.C. §403), the Magnuson-Stevens Fishery Conservation and Management Act (16 U.S.C. §1801 et seq, as amended by the Sustainable Fisheries Act), the Lacey Act (16 U.S.C. §3371), the Endangered Species Act (16 U.S.C. §1531 et seq.), and the Non-Indigenous Aquatic Nuisance Prevention and Control Act (16 U.S.C. §4701 et seq.). The federal government also provides research and other assistance to the aquaculture industry through the National Aquaculture Act (16 U.S.C. §2801) and the Joint Subcommittee on Aquaculture (see http://ag.ansc.purdue.edu/aquanic/jsa).

Army Corps of Engineers Permit Process

Any company wanting to operate an aquaculture facility in navigable waters, the location of virtually all net-pen salmon facilities, needs a permit from the Army Corps of Engineers (ACOE). The ACOE licenses such facilities under regulations issued under the Rivers and Harbors Act (33 CFR Part 320). In general, the ACOE, in evaluating permit applications, applies a balancing test among such factors as conservation, economics, the environment, fish and wildlife values, recreation and navigation concerns, and consideration of property ownership. This process includes public notice and the opportunity for public hearings, which generally occur at a regional level. During its consideration of a permit application, the ACOE consults with agencies such as FWS, NMFS, or the EPA. During this consultation process, the ACOE may impose conditions and post-approval monitoring and reporting requirements for such issues as escapes, inventory tracking, and environmental monitoring.

While this process includes consideration of environmental effects and allows for public input, none of the agencies appear to have clear legal authority to block an aquaculture project on the basis of its risk to fish habitat, unless the fish at risk are listed under the Endangered Species Act (ESA). While the ACOE can and does impose conditions on permits to address environmental risks, its principal focus is ensuring that a fish pen itself is structurally sound and does not affect navigation as required by the Rivers and Harbors Act. Although the National Environmental Policy Act (NEPA) ensures the disclosure of environmental risks, this process-based statute does not alter the statutory basis for decision-making. Similarly, the Magnuson-Stevens Fishery Conservation and Management Act, which protects fish stocks, does not give NMFS the authority to impose its recommendations on the ACOE; it requires only consultation (see 67 Fed. Reg. 2343, January 17, 2002).

If a proposed project were to trigger the Endangered Species Act by jeopardizing a species or its critical habitat, then NMFS or FWS could intervene to block it. For example, given that Atlantic salmon are a listed species (65 Fed. Reg. 65459, November 17, 2000; 50 C.F.R. Part 224 and Part 17), NMFS or FWS may have the authority to impose restrictions on or to prohibit the ACOE's granting of permits to aquaculture operations utilizing transgenic salmon. However, developers are creating many other types of transgenic fish that do not trigger the ESA. For example, scientists are developing genetically modified tilapia or channel catfish, which are not threatened or endangered, and developers may not necessarily raise them in net-pens requiring an ACOE permit.

Other Approaches to Address Environmental Risks

The Clean Water Act requires aquaculture facilities to obtain discharge permits from EPA or the states. This regulatory program currently focuses on effluent discharge and does not address issues related to transgenic fish. The EPA is in the process of establishing a national discharge program specifically for aquaculture, which they expect to finalize by 2004.

A number of other statutes could, theoretically, be applied to address issues related to transgenic fish. For example, the Lacey Act and the Non-Indigenous Aquatic Nuisance Prevention and Control Act provide the DOI with authority to address and control the risk of non-indigenous species. These acts have been cited as a potential basis for the assertion of federal regulatory authority over the environmental aspects of transgenic fish (CEQ-OSTP 2001). However, there has been little public guidance or agency discussion as to how these laws might be applied to address the risks presented by transgenic fish and there would appear to be significant legal questions about their application.

Option 2: TSCA Approach

A second possible legal basis for review of the environmental impacts of transgenic fish could come under the Toxic Substances Control Act (TSCA). TSCA gives the EPA the authority to review "new chemical substances" which may present an unreasonable risk of injury to human health or the environment (15 U.S.C. §2601 et seq.). TSCA applies to uses of substances not specifically covered by another statute (e.g., food, pesticides regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), or drugs regulated under FFDCA). TSCA defines a "chemical substance" as "any organic or inorganic substance of a particular molecular identity." The EPA has interpreted the definition broadly to include biological organisms. For example, the EPA has exercised jurisdiction and issued regulations on genetically modified microorganisms (40 CFR Part 725). The EPA has also claimed that the Act gives it authority to regulate genetically modified animals (CEQ-OSTP 2001). Since TSCA explicitly exempts food or drugs, EPA would presumably have to regulate transgenic fish by claiming jurisdiction over the genetic construct used to modify the fish. (In a similar fashion, the EPA has construed its authority to regulate pesticides under FIFRA to extend to the pesticide produced by the plant tissues of genetically modified plants, although the plants themselves do not fall under its legal authority.) To date, the EPA has not attempted to exercise this claim, and there is some question whether a court would sustain that interpretation.

Assuming TSCA were applied to transgenic fish, it would likely require developers to submit a precommercial notification to the EPA. The EPA would then review the data submitted to assess the potential for an "unreasonable risk" to human health and the environment. While the EPA could presumably consider the impacts of escapes on wild fish populations, TSCA also clearly contemplates a weighing of benefits and risks in determining what constitutes an "unreasonable" risk. Moreover, the burden lies not with the developer to prove safety; but rather with the EPA to prove the product would create an "unreasonable risk" to the environment. Unless the EPA finds such a risk, the product may proceed to market.

Option 3: New Animal Drug Authority

As noted previously, the FDA has indicated its intention to review both the food safety and environmental impacts of transgenic animals, including fish, under the animal drug approval provisions of the FFDCA. The following discussion details the implications of this choice.

C POLICY ISSUES:

FDA'S NEW ANIMAL DRUG APPROACH TO TRANSGENIC FISH

The FDA's choice of the "new animal drug" approval provisions as the principal means to review both the food safety and environmental risks of transgenic animals, including fish and other aquatic organisms, raises several significant policy issues. It also illustrates some of the challenges created by the application of existing laws to new technologies.

In some respects, this choice of legal authority is not as long a stretch as it might first seem. Under the FFDCA, the FDA has the authority to approve any conventional drug that would increase growth hormone levels in a fish. Achieving the same end through genetic modification should therefore receive similar scrutiny. However, as discussed below, there are significant differences between a traditional animal drug and genetic modifications, which raise questions about the adequacy and "fit" of the new animal drug approval provisions for reviewing transgenic animals. The use of the new animal drug approval provisions to regulate transgenic fish raise issues, with both benefits and drawbacks, in five particular areas:

- legal authority;
- adequacy of risk management tools;
- transparency, clarity, and public participation;
- resources and expertise; and
- efficiency and coordination.

a. Legal Authority

Food Safety. Under the FFDCA, a sponsor cannot sell a new animal drug on the market until it has demonstrated that:

i) the drug is effective;
ii) it is safe for the target animal;
iii) it is safe for humans to consume food derived from the treated animal;
iv) it will not cause undo harm to the environment;
v) it is safe for a user to handle;
vi) it is clearly labeled to communicate noteworthy risks; and
vii) a summary of data has been made available as required by the Freedom of Information Act.

Among other things, the sponsor must demonstrate through "adequate tests by all methods reasonably applicable" that the drug is "safe for use under the conditions prescribed." As noted earlier, with respect to food safety, the sponsor must meet the same standard as the food additive standard and demonstrate a "reasonable certainty of no harm" (CEQ-OSTP 2001).

If the FDA is correct that the genetic constructs inserted into an animal through biotechnology and their expression products meet the statutory definition of a "new animal drug," then the FFDCA appears to set out clear standards and give the FDA adequate authority to ensure that these constructs do not affect the safety of the food derived from the modified animals.

Environment. The FFDCA contains no provisions expressly dealing with environmental risks. Instead, its concern lies with safety as it relates to "health of man or animal." As applied to conventional animal drugs, the Act intends to ensure that the drug, when used as prescribed, does not harm the health of the animal. However, the FDA has interpreted this provision broadly to include environmental effects that could directly or indirectly effect the health of the animal itself, as well as other animals not treated with the drug.[6] In other words, the FDA could interpret environmental harm as posing "risk to the health of man or animal" and deny an application on that basis.

The "animal" referenced in the statute, however, typically means the animal on which the drug will be used. But in the case of transgenic fish, the key issue is not the health of the transgenic fish itself, but the effects of the release of transgenic fish on wild fish populations. The FDA agrees that it cannot consider environmental impacts that have no health risk, such as an environmental impact that would detract from scenic beauty (CEQ-OSTP 2001). Some of the potential environmental impacts of transgenic fish—including harm to centers of species origin and other genetic resources or a decline in fish community resilience—would appear to fall into that category. It is uncertain whether the FDA could exercise its authority to prevent, reduce, or mitigate such consequences.

[6] In the approval process for recombinant bovine somatotropin (rBST), a hormone made by genetically modified bacteria, the FDA expressly considered broad environmental risks that could potentially be presented through the use of the drug. For example, the FDA considered the possibility that approval of the drug (1) might affect land-use patterns and water quality by affecting the types of feed ingredients grown for dairy cows, (2) might affect carbon dioxide emissions due to changed ration requirements and dairy populations, and (3) might present a used syringe disposal problem (CEQ-OSTP 2001). The FDA's authority to consider these environmental impacts was not challenged in the process. The FDA approved rBST as a new animal drug in 1993.

In addition, it is unclear what legal standards would apply to these environmental risks. The standard of "reasonable certainty of no harm" applies a fairly clear standard for food safety issues, but no similarly clear standard exists in the statute for environmental risks. Is any level of possible environmental harm too much? What constitutes an acceptably "safe" level? Could the FDA consider potential offsetting environmental benefits—such as reduced water pollution loadings or impacts on over-fished ocean areas?

The National Environmental Policy Act (NEPA) does not give the FDA substantive authority to prevent or manage environmental risks from transgenic organisms, nor to clarify the standards that the agency will apply. As noted earlier, while NEPA gives the FDA the *procedural* responsibility to assess environmental impacts of proposed agency actions, it does not give it the *prescriptive* authority to disallow certain kinds or magnitudes of environmental impact. In other words, even if the FDA issues an environmental impact statement in connection with a new animal drug application that identifies serious environmental concerns, NEPA does not give the FDA the authority to *deny* a new animal drug application on environmental grounds.

Courts have traditionally granted the FDA significant deference in interpreting the FFDCA, but a critical question remains whether the FDA has a legally defensible basis for regulating at least some of the environmental aspects of transgenic fish. Further, the legal standards needed to demonstrate "safety" with respect to environmental issues are unclear. The FDA's assertion of jurisdiction to address environmental risks may be susceptible to challenge if the FDA were to deny an application for a transgenic fish on environmental grounds alone. However, experts have speculated that developers of transgenic aquatic organisms will voluntarily comply with FDA regulation, even if they have questions about its enforceability.

b. Adequacy of Risk Management Tools

Provided the FFDCA gives the FDA the legal authority to regulate transgenic fish for food safety and environmental concerns, it becomes important to determine if the statute also gives the FDA sufficient tools to manage those risks.

The FFDCA's new animal drug approval provisions are broad, flexible, and afford the agency a great deal of authority *before* and *after* the new product approval. In the pre-approval phase, the FFDCA requires product developers to prove the safety of the product. The FDA enforces this by insisting developers gather and submit data demonstrating a product's safety. (Unlike the developers of genetically modified crops, developers of genetically modified animals, including fish, will have to comply with this requirement and demonstrate the food safety of transgenic animals prior to their marketing.) The agency also has substantial powers to impose conditions and restrictions on the use of the product, including labeling and post-approval monitoring and studies. Lastly, the FFDCA enables the FDA to require companies to report adverse effects identified after the product is approved and marketed. If necessary, the FDA has the authority to stop the marketing of a particular product. Combined, these provisions give the FDA sound tools to enforce the management of risks associated with genetically modified animals —provided the FFDCA gives it the authority to regulate them as new animal drugs.

c. Transparency, Clarity, and Public Participation

Transparency, clarity, and public participation are related elements in a regulatory process that aims to ensure public credibility and confidence in an agency decision. Credibility and confidence are particularly important with respect to new technologies, especially for controversial ones like biotechnology. As the FDA has noted, "[p]ublic acceptance of foods derived from transgenic animals will be important to the success of any transgenic variety introduction" (Matheson, 2000). Critical to public acceptance is confidence in an agency's determination of the safety of these foods for consumers and the environment.

Transparency is the ability of the public to review the basis of an agency decision. Ideally, agencies would make publicly available both the critical data it has relied upon, as well as the rationale for its decision. Transparency helps ensure a sound agency decision by subjecting it to public review, as well as ensuring the integrity of the process by disclosing the critical information upon which the agency relied. While it is preferred that critical information be disclosed before an important decision is made, even disclosure after the fact can act as an important check on agency action.

Clarity is related to transparency. The public needs to understand not only the basis for an agency decision, but also the process for reaching that decision. If the regulatory process is uncertain, unpredictable, and unclear, it also makes it difficult for industry to make informed decisions and understand in advance FDA requirements for approving a new transgenic animal. Similarly, lack of clarity makes it difficult for the public to know in advance the FDA's decision-making rules for its determinations and could jeopardize the credibility of the agency's decision.

Public participation can take a number of forms. The key element is an opportunity for the public to have input into an agency decision-making process before a decision is made. Participation helps to ensure the openness and integrity of the regulatory process and can provide an important mechanism to correct or supplement the data upon which the agency is relying.

The amount of transparency and public participation in any given regulatory proceeding varies widely, depending both on the law under which the FDA is proceeding as well as procedures and regulations issued by the FDA. There is often a need to strike a balance between public disclosure and protection of confidential business information protected by law. Some FDA decisions provide for significant transparency and participation through notice and comment procedures, by providing access to agency materials under the Freedom of Information Act, and by holding open meetings where public input is invited. Some FDA decisions regarding products under its jurisdiction also provide opportunities for public input prior to final action. For example, food additive petitions and petitions seeking an Agency determination that a particular food is safe and, therefore, not subject to pre-market approval are both subject to notice and comment procedures. Materials relating to such petitions are generally available for public inspection prior to agency action.

However, the new animal drug application process is much more closed. The FDA has interpreted the FFDCA to prohibit disclosure of information related to certain FDA actions,[7] including agency consideration of new animal drug applications. As a result, all of the data and information related to the application, including the very fact the application has been filed, is kept confidential throughout the entire review process, unless the sponsor makes information available to the public. If the FDA denies the new animal drug application, this information remains confidential. Only after the FDA grants a new animal drug application may it release the information. Even then, it makes public only portions of the file. The practical effect is that even after the FDA approves an application, much of the information submitted as part of that application, or any earlier underlying information from an investigational application, remains undisclosed.

This closed process may have merit for protecting the intellectual property involved in the traditional human or animal drug approval. When applied to transgenic animals, however, it blocks public consideration of, and input into, a range of policy issues that go beyond technical and scientific considerations of safety. In particular, questions about what constitutes an acceptable level of environmental risk are at least as much policy questions as they are scientific questions. The public cannot even know, unless the sponsor chooses to disclose it, what types of transgenic animals are pending approval. This lack of transparency and public participation in the new animal drug approval process significantly challenges an agency hoping to retain public confidence in its decision-making process.

The FDA itself has recognized that the confidential nature of the new animal drug approval process creates a conflict with the National Environmental Policy Act (NEPA). FDA regulations require new animal drug applications to include an environmental assessment (EA) to help determine if the product would have significant enough environmental impact to require a full Environmental Impact Statement (EIS) before approval. Ordinarily, NEPA requires a public airing of an agency's consideration of significant environmental impacts posed by the prospective agency action (42 U.S.C. §4341). Current FDA regulations prevent it from making an EA public before the final decision. The FDA has noted that: "The agency recognizes the difficulty this poses in ensuring a public process for evaluating possible environmental risks associated with any particular transgenic modification of a fish species and is considering what options it might have to address this situation" (CEQ-OSTP 2001).

[7] This position is largely driven by the regulations that require the protection of confidential business information and trade secrets.

The novel application of the "new drug approval" provisions of the FFDCA to transgenic animals, with the broad regulatory authorities given to the FDA under the Act, combine to create significant uncertainty about how the FDA will apply the law's provisions in practice. In numerous cases, the many differences between a traditional new animal drug, which typically involves the administration of a chemical substance to an animal, and a transgenic animal, whose altered DNA affects the animal's chemical functioning, raises many questions about the "fit" of existing agency rules and practices for addressing transgenic issues.

For example, the safety assessment for a traditional new animal drug addresses the safety of a specific compound—safety for the animal and safety of the meat or milk. Safety questions raised by alterations to an animal's genome, however, may extend beyond the safety of the new "drug" itself. Without a clear description of what safety elements the FDA is considering as part of the new animal drug application process, it is difficult to assess the comprehensiveness of the review process.

Similarly, the Agency has noted that its evaluation of human food safety in the new animal drug context assumes that "the drug product in question will be manufactured consistently from one batch to the next to the same standards of purity, strength and identity as the product used to generate the human food safety data" (Food and Drug Administration 2001a). When applied to transgenic fish, however, this assumption can prove problematic. Does a "batch" consist of a single fish or a transgenic line? Can the FDA guarantee the "consistent" manufacture of the drug, given it has little control of the genetic evolution that may (or may not) occur at reproduction? Sponsors seeking to demonstrate human food safety of their animal drug often provide data on the time period required after cessation of drug treatment for drug residues to reach safe levels. In the context of transgenic fish, no equivalent cessation of treatment exists, because the protein expressed by the transgene is produced on a continuous basis.

Perhaps the greatest area of uncertainty about the approval process concerns the process by which the FDA will evaluate the environmental risks presented by transgenic fish. Earlier in this report it was explained how a net fitness assessment could be used to develop hypotheses concerning the potential effect of transgenic fish on an ecosystem. It is unclear whether the FDA will use this or any model when evaluating transgenic fish, and it is even less clear whether the FDA has the staff expertise needed to use the model. Further, the FDA has not yet gathered public input on the development of criteria with which to judge whether the environmental risks of a particular transgenic fish are acceptable. The FDA has indicated its intention to publish for comment a draft guidance document describing its approach to conducting environmental assessments of transgenic salmon, but has not yet done so. The FDA may have difficulty providing guidance that will apply broadly, given that many of the risks (and therefore the data needed to assess them) will vary on a case-by-case basis. For example, the question of determining net fitness, as discussed in Section II, will turn on the individual characteristics of the transgenic species and the specifics of the environment into which they might escape. Indeed, with respect to food safety issues, the Center for Veterinary Medicine (CVM) within the FDA has indicated that human food safety programs will likely be established on a case-by-case basis in conjunction with manufacturers (Miller and Matheson 1996).

Without more clear and public guidance, however, questions remain about the FDA's approval process. How will the FDA measure and account for risks? Will the FDA assess the net fitness of each particular strain of GM salmon in a particular ecosystem, (which may be necessary since each strain may present different risks in different ecosystems)? For example, a transgenic salmon escaping into an ecosystem that lacks a robust native population may present a greater risk of becoming an invasive species than if it escaped into an ecosystem with a robust native population. If the escape of transgenic fish from net pens is inevitable, will the FDA either define an acceptable number of escapes or impose restrictions on production (i.e., either require all sterile females in net pens, or restrict use of non-sterile or sterile males to closed systems)? In other words, how will the FDA define a level of "acceptable risk" of escape or genetic introgression? Will there be an opportunity for public dialogue to discuss what may or may not be an acceptable risk?

In addition, genetically modified fish pose challenges relative to post-approval monitoring and reporting. For example, in the drug approval situation, the FDA can require companies to report to the agency if problems occur, allowing removal from the market, if necessary. How will the FDA define an adverse or reportable event? Is it one or one thousand or one hundred thousand escaped fish? In any case, is it possible to remove an escaped fish from the environment or retrieve a gene that has introgressed into a native population?

This lack of clarity and predictability in the FDA's application of the new drug approval process to transgenic animals provides neither the industry nor the public with a clear set of rules to follow. Without such road map, it is difficult for the public to trust that the development of transgenic animals is being handled in a thoughtful, uniform manner, and it may potentially weaken public confidence in the agency's final regulatory decision.

d. Resources and Expertise

If the FDA were able, as a matter of law, and willing, as a matter of practice, to incorporate environmental concerns in its new animal drug review, it is unclear whether the agency has the expertise to evaluate the environmental effects of new animal drugs. This is especially true of the kinds of complex and often novel environmental effects associated with genetically modified fish. A number of federal agencies, including the Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS) are charged statutorily with addressing the environmental impacts of aquatic species and animals generally, and possess expertise in this area that the FDA may lack. The FDA has recognized the need to consult with these other resource agencies, but has not announced a clear coordinating framework of how these agencies will be involved on a consistent basis (CEQ-OSTP 2001).

Without an articulated framework, it is uncertain whether the FDA will have sufficient resources and expertise available to fully evaluate and address these risks. Moreover, important questions regarding environmental risks may require public input. Given the difficulty of public disclosure associated with new animal drug approval applications, it may be difficult to assure the public that the relevant agencies are in fact at the table ensuring that the necessary studies and evaluations for assessing and addressing environmental risks are conducted prior to approval.

e. Efficiency and Coordination

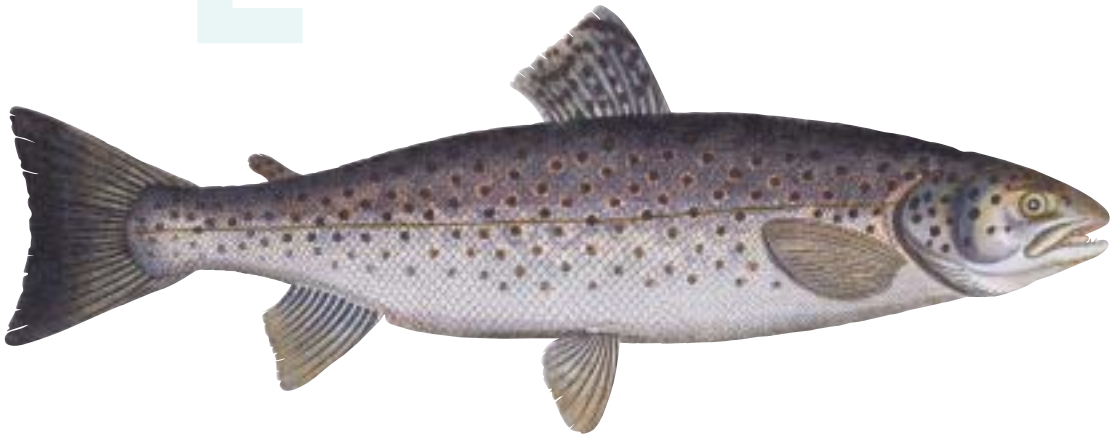
As discussed earlier, a number of laws may provide the basis for regulating transgenic organisms, both for food safety and environmental concerns. In addition, the expertise to deal with food safety and environmental risks associated with transgenic animals is also spread over several federal agencies. The CEQ-OSTP Case Studies constitute the only document showing how the federal government intends to review transgenic animals. (CEQ-OSTP 2001). Although these case studies provide important guidance as to how the various agencies may regulate transgenic fish, the report explicitly states that it does not establish new policies or procedures. Although public comments were received on the CEQ-OSTP Case Studies, there is no unified federal regulatory approach that reflects public input and informs the public how the various federal agencies will coordinate their efforts and apply their respective authorities to address the risks of transgenic fish. In the absence of a clear statement of how these authorities and agencies will work together, it is difficult to judge whether the regulatory system for reviewing transgenic animals is efficient, sufficient, and well coordinated.

On the one hand, combining the federal government's review of both food safety and environmental concerns into a single agency proceeding would be an efficient process. On the other hand, as noted above, it is unclear how other agencies with environmental expertise will be involved in that decision-making process. Further, in the absence of a clear federal approach, questions remain on whether other agencies retain the authority to consider impacts of transgenic fish regardless of the FDA's actions under the new animal drug approval process. Should the Army Corps of Engineers take into account concerns about the potential impact of transgenic escapes on wild fish populations when permitting aquaculture facilities? Should the EPA attempt to regulate transgenic fish by defining the potential escape or release of such fish as biological pollution under a national effluent discharge permit program for aquaculture? Or should transgenic fish be considered and regulated as non-indigenous invasive species? While some authority exists for such an approach, critics may point out that, to date, the government has not done an effective job regulating invasive species and may question whether the agencies could adequately address the risks of transgenic fish. An efficient regulatory system should seek to avoid multiple agencies' reviews under competing regulatory schemes.

chapter

FIVE

Conclusion: Regulatory Policy Issues



chapter 5

CONCLUSION: REGULATORY POLICY ISSUES

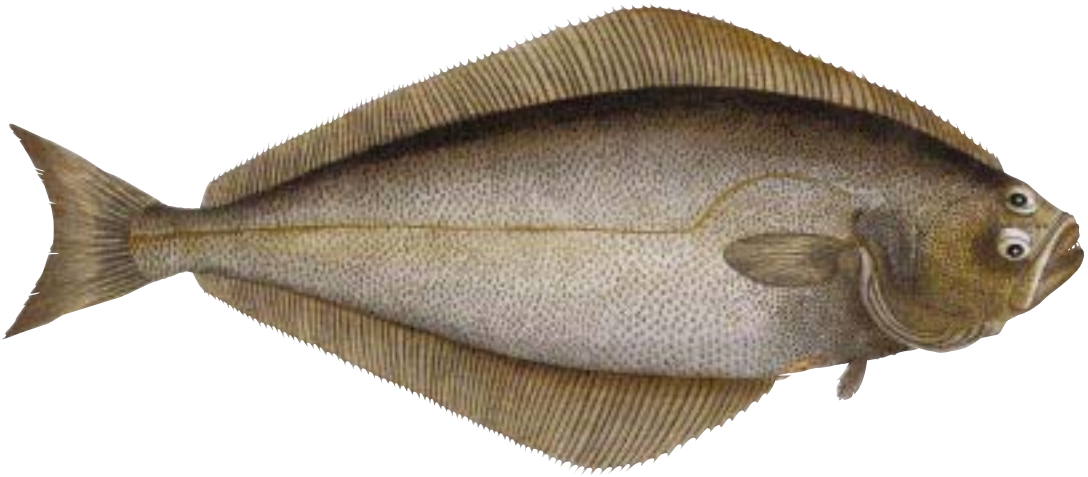
A central principle governing the federal government's regulatory approach to biotechnology products is that existing authority is sufficient to oversee the public health and safety issues that biotechnology may present. As the technology advances, however, the challenges of fitting new biotechnology applications into existing statutory schemes will likely become more problematic.

Transgenic fish provide a case in point. In theory, regulators could review possible food safety and environmental risks of transgenic fish under a number of laws. Also, the expertise for considering such issues is spread over several federal agencies. The FDA's assertion of authority and its use of the new animal drug approval provisions in FFDCA have significant implications for the regulation of transgenic fish and other animals. In some respects, the choice is appropriate. The FDA clearly has the expertise to ensure both the safety of food derived from transgenic animals and that the drug (or genetic modification) does not harm the animal. Its pre-market approval process ensures a full consideration of those issues before a developer can bring a product to market.

But the FDA is only one of several agencies that could lead the regulatory review process of transgenic fish. The fact that it has stepped forward first and asserted its authority does not necessarily mean it is the most appropriate agency to do so. The FFDCA does not comfortably cover all the key issues that must be addressed when evaluating the safety of transgenic fish. Unlike conventional animal drugs, genetically modified fish carry the "drug" from generation to generation. The "drug" cannot stop being administered if the modified fish escape into an uncontrolled environment. As a result, environmental issues arising from gene flow—issues not associated with conventional animal drugs—must also be considered. The new animal drug approval authority seems least appropriate here. The FDA's legal authority to consider environmental risks beyond harm to the modified animal itself is uncertain at best. The agency also lacks the expertise to consider ecological risks, such as those that might be posed by the escape of transgenic fish. Its closed, confidential process does not permit public input into the environmental assessment process and is unlikely to

generate public confidence in the agency's decisions. In addition, the lack of clear guidance to date about how the FDA intends to implement the FFDCA with respect to transgenic animals creates uncertainty for businesses as well as for the public. Finally, it is unclear whether the FDA's assertion of authority over the environmental impacts of transgenic fish is the exclusive means of reviewing such risks, or whether other existing authorities might also be used. For example, it is not clear whether the Army Corp of Engineers would consider the potential impacts of escaped transgenic fish on wild fish populations as part of the process for permitting aquaculture facilities.

While the FDA's use of the new animal drug approval authority for regulating transgenic fish addresses food safety issues and provides some opportunity to consider and address environmental risks, the current regulatory approach is an ad-hoc extension of existing regimes. The proposed regulation of transgenic fish does not reflect a unified federal strategy to address the risks of genetically modified fish in a transparent manner that provides public confidence that these risks will be adequately considered and addressed.



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Selected References

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SELECTED REFERENCES

Agricultural Biotechnology Research Advisory Committee, Working Group on Aquatic Biotechnology and Environmental Safety. 1995. *Performance Standards for Safely Conducting Research with Genetically Modified Fish and Shellfish, Parts I and II*. Blacksburg, VA: Information Systems for Biotechnology. Available at www.isb.vt.edu/perfstands/prntstands.cfm.

Berkowitz, D. B. and I. Krypsin-Sørensen. 1994. Transgenic fish: safe to eat? *Bio/Technology* 12:247-252.

Biotechnology Risk Assessment Research Grants Program, United States Department of Agriculture. 2001. *Research Awards—Fiscal Year 2000*. Washington, D.C.: United States Department of Agriculture. Available at www.reeusda.gov/crgam/biotechrisk/biot001s.htm.

Busack, C. A. and K. P. Currens. 1995. Genetic risks and hazards in hatchery operations: fundamental concepts and issues. *American Fisheries Society Symposium* 15:71-80.

Byers, J. 2000. Competition between two estuarine snails: implications for invasions of exotic species. *Ecology* 81(5):1225-1239.

Carr, J. W., J. M. Anderson, F. G. Whoriskey, and T. Dilworth. 1997. The occurrence and spawning of cultured Atlantic salmon (*Salmo salar*) in a Canadian river. *ICES Journal of Marine Science* 54:1064-1073.

Center for Biologics Evaluation and Research, Food and Drug Administration. 1995. *Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals.* Rockville, MD: Center for Biologics Evaluation and Research. Available at www.fda.gov/cber/gdlns/ptc_tga.txt.

Center for Food Safety. 2001. *Petition Seeking A Moratorium On the Domestic Marketing And Importation of Transgenic Fish*. Citizen Petition Before the United States Food and Drug Administration. Rockville, MD: Dockets Management Branch. Available at www.centerforfoodsafety.org/gefish/legal/fda/fda_petition.htm.

Center for Veterinary Medicine, Office of New Animal Drug Evaluation, Food and Drug Administration. 1989. *Target Animal Safety Guidelines for New Animal Drugs, Guideline 33*. Rockville, MD: Center for Veterinary Medicine. Available at www.fda.gov/cvm/guidance/guideline33.html.

Center for Veterinary Medicine, Food and Drug Administration. 2001. "Import Tolerances, Advanced Notice of Proposed Rulemaking." *Federal Register* 66 (155) (10 August 2001):42167-42170.

Chatakondi, N., R. Lovell, P. Duncan, M. Hayat, T. Chen, D. Powers, T. Weete, K. Cummins, and R. A. Dunham. 1995. Body composition of transgenic common carp, Cyprinus carpio, containing rainbow trout growth hormone gene. *Aquaculture* 138(1-4):99-109.

Committee on Protection and Management of Pacific Northwest Anadromous Salmonids. 1996. *Upstream: Salmon and Society in the Pacific Northwest*. Washington, D.C.: National Academy Press.

Cook, J. T., M. A. McNiven, G. F. Richardson, and A. M. Sutterlin. 2000. Growth rate, body composition, and food digestibility/conversion of growth-enhanced Atlantic salmon *(Salmo salar)*. *Aquaculture* 188 (1-2):15-32.

Cotter, D., V. O. Donovan, N. O'Maioleidigh, G. Rogan, N. Roche, and N. P. Wilkins. 2000. An evaluation of the use of triploid Atlantic salmon (*Salmo salar* L.) in minimizing the impact of escaped farmed salmon on wild populations. *Aquaculture* 186:61-75.

Council on Environmental Quality and Office of Science and Technology Policy (CEQ-OSTP). 2001. *Case study No. 1: 1Growth enhanced salmon*. Case Studies of Environmental Regulation for Biotechnology: Washington, D.C.: Office of Science and Technology Policy. Available at www.ostp.gov/html/ceq_ostp_study2.pdf.

de Gaudemar, B. 1998. Sexual selection and breeding patterns: insights from salmonids (salmonidae). *Acta Biotheoretica* 46:235-251.

Devlin, R. H., Unpublished data. Department of Fisheries and Oceans Canada.

Devlin, R. H., T. Y. Yesaki, C. Biagi, E. M. Donaldson, W. K. Chan. 1994. Production and breeding of transgenic salmon. In *Proceedings, 5th World Congress on Genetics Applied to Livestock Production 19*, edited by C. Smith, et al., 372-278. University of Guelph, Guelph, Ontario, Canada.

Devlin, R. H., C. A. Biagi, T. Y. Yesaki, D. E. Smalius, and J. C. Byatt. 2001. Growth of domesticated transgenic fish. *Nature* 209 (15 February):781-782.

Devlin, R. H., J. I. Johnsson, D. E. Smalius, C. A. Biagi, E. Jönsson, and B. Th. Björnsson. 1999. Increased ability to compete for food by growth hormone-transgenic coho salmon *Oncorhynchus kisutch* (Walbaum). *Aquaculture Research* 30:479-482.

Di Castri, F. 1989. History of biological invasions with special emphasis on the Old World. In *Biological Invasions: A Global Perspective*, edited by J. A. Drake et al., 1-26. New York: John Wiley.

Donaldson, E.M. and R. H. Devlin. 1996. Uses of biotechnology to enhance production. In *Developments in Aquaculture and Fisheries Science*, No. 29, edited by W. Pennell and B. A. Barton, 969-1020. Amsterdam: Elsevier Publishers.

Dunham, R.A., J. Eash, J. Askins, and T.M. Townes. 1987. Transfer of the metallothionein-human growth hormone fusion gene into channel catfish. *Transactions of the American Fisheries Society* 116:87-91.

Dunham, R.A., C. Chitmanat, A. Nichols, B. Argue, D.A. Powers, and T.T. Chen. 1999. Predator avoidance of transgenic channel catfish containing salmon growth hormone genes. *Marine Biotechnology* 1:545-551.

Dunham, R.A., G.W. Warr, A. Nichols, P.L. Duncan, B. Argue, D. Middleton, and H. Kucuktas. 2002. Enhanced bacterial disease resistance of transgenic catfish Ictalurus punctatus possessing cecropin genes. *Marine Biotechnology*.

Environmental Protection Agency. 2002. Volunteer Estuary Monitoring: A Methods Manual, Chapter 12: Toxins. Washington, D.C.: Office of Wetlands, Oceans and Watersheds. Available at http://www.epa.gov/owow/estuaries/monitor/chptr12.html.

Faulkner, D. J. 1993. Marine natural products. *Natural Products Reports* 10(5):497-539.

Fisk, P. and R. A. Lund. 1999. Escapees of reared salmon in coastal and riverine fisheries in the period 1989-1998. *NINA Offdragsmelding* 603:1-23 (in Norwegian with an English abstract).

Fleming, I. A. 1996. Reproductive strategies of Atlantic salmon: ecology and evolution. *Reviews in Fish Biology and Fisheries* 6:379-416.

Fleming, I. A. 1998. Pattern and variability in the breeding system of Atlantic salmon (*Salmo salar*), with comparisons to other salmonids. *Canadian Journal of Fisheries and Aquatic Sciences* 55 (Suppl. 1):59-76.

Fletcher, G. L. et al. 1996. U.S. Patent and Trademark Office, patent #5,545,808.

Fletcher, G. L., M. A. Shears, and S. V. Goddard. 1999. Transgenic fish for sustainable aquaculture. In *Sustainable Aquaculture*, edited by N. Svennig, H. Reinertsen, and M. New, 193-201. Rotterdam: Balkema.

Food and Agricultural Organization of the United Nations (FAO). 2000. *FAO Yearbook of Fishery Statistics: Aquaculture Production.* FAO Fisheries Series. Rome, Italy: Food and Agricultural Organization of the United Nations.

Food and Agricultural Organization of the United Nations (FAO). 2000a. *The State of World Fisheries and Aquaculture 2000*. Rome, Italy: Food and Agriculture Organization of the United Nations.

Food and Drug Administration. 1982. Memorandum of understanding between the Animal and Plant Health Inspection Service and the Food and Drug Administration, Department of Health and Human Services, August 15, 1982. Compliance Policy Guidelines, Guide 71551.17, Chapter 55a – MOUs and IAGs – Federal. Issued by EDRO, Compliance Guidelines Branch, DFRG, Associate Commissioner for Regulatory Affairs.

Food and Drug Administration. 1992. "Statement of Policy: Foods derived from new plant varieties." *Federal Register* 57 (29 May 1992): 22984-23005. Available at http://vm.cfsan.fda.gov/~lrd/bio1992.html.

Food and Drug Administration. 2001. "Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering." *Federal Register* 66 (18 January 2001):4839-4842. Available at www.fda.gov/OHRMS/DOCKETS/98fr/011801c.htm.

Food and Drug Administration. 2001a. "Advance notice of proposed rulemaking: Import Tolerances." *Federal Register* 66 (10 August 2001): 42167-42170. Available at http://www.fda.gov/OHRMS/DOCKETS/98fr/081001a.htm.

Forster, J. 1999. Aquaculture chickens, salmon—a case study. *World Aquaculture* 30(3) (September): 33-38, 40, 69-70.

Fu, C., Y. Cui, S. S. O. Hung, and Z. Zhu. 1998. Growth and feed utilization of F4 human growth hormone transgenic carp fed diets with different protein levels. *Journal of Fish Biology* 53:114-129.

Gibbons, M. 1999. Science's new social contract with society. *Nature* 402, Suppl. 2, (December):C81-C84.

Gido, K. B. and J. H. Brown. 1999. Invasion of North American drainages by alien fish species. *Freshwater Biology* 42:387-399.

Goldburg, R. and T. Triplett. 1997. *Murky Waters: Environmental Effects of Aquaculture in the US.* Washington, D.C.: Environmental Defense Fund. Available at www.environmentaldefense.org / documents / 490_AQUA.PDF.

Goldburg, R. J., M. S. Elliott, and R. L. Naylor. 2001. *Marine Aquaculture in the United States: Environmental Impacts and Policy Options.* Arlington, VA: Pew Oceans Commission.

Goldschmidt, T. 1996. *Darwin's Dreampond: Drama in Lake Victoria*. Cambridge, MA: MIT Press.

Gross, M. 1998. One species with two biologies: Atlantic salmon (*Salmo salar*) in the wild and in aquaculture. *Canadian Journal of Fisheries and Aquatic Sciences* 55 (Suppl. 1):131-144.

Gross, M. 2001. Potential impact of fish farming on wild salmon in British Columbia. In *The Swimmers: The Future of Wild Salmon on the North and Central Coasts of British Columbia*, 107-117 Victoria, B. C., Canada: Raincoast Conservation Society.

Guillén, I., J. Berlanga, C. M. Valenzuela, A. Morales, J. Toledo, M. P. Estrada, P. Puentes, O. Hayes, and J. de la Fuente. 1999. Safety evaluation of transgenic tilapia with accelerated growth. *Marine Biotechnology* 1:2-14.

Gura, T. 2000. Reaping the genetic harvest. *Science* 287 (21 January):412-414.

Hallerman, E. M. 2002. Commercialization of genetically modified fish and shellfish: issues for Virginia. *Virginia Issues and Answers* 8(1):10-17

Hallerman, E. M., and A. R. Kapuscinski. 1990. Transgenic fish and public policy. Patenting of transgenic fish. *Fisheries* 15(1):21-24

Hallerman, E. M. and A. R. Kapuscinski. 1992. Ecological implications of using transgenic fishes in aquaculture. *International Council for the Exploration of the Seas Marine Science Symposia* 194:56-66

Hedrick, P. W. 2001. Invasion of transgenes from salmon or other genetically modified organisms into natural populations. *Canadian Journal of Fisheries and Aquatic Sciences* 58:841-844.

Hew, C. L., G. L. Fletcher, and P. L. Davies. 1995. Transgenic salmon: tailoring the genome for food production. *Journal of Fish Biology* 47 (Supplement A):1-19.

Inada, Y. and N. Taniguchi. 1991. Spawning behavior and after-spawning survival in induced triploid ayu *Plecoglossus altivelis*. *Bulletin of the Japanese Society of Science and Fisheries* 57:2265-2269.

Inland Water Resources and Aquaculture Service. 1997. *Review of the State of World Aquaculture*. Rome, Italy: Food and Agriculture Organization of the United Nations.

Iso, H., K. M. Rexrode, M. J. Stampfer, J. E. Manson, G. A. Colditz, F. E. Speizer, C. H. Hennekens, and W. Willett. 2001. Intake of Fish and Omega-3 Fatty Acids and Risk of Stroke in Women. *Journal of American Medical Association*. 285: 304-312.

International Food Information Council (IFIC). 2002. *Fish and Your Health*. Washington, D.C.. Available at http://www.ific.org/pdf/FishandHealthBrochure.pdf.

Johnsson, J. I., E. Petersson, E. Jönsson, T. Järvi, and B. Th. Björnsson. 1999. Growth hormone-induced effects on mortality, energy status and growth: a field study on brown trout (*Salmo trutta*). *Functional Ecology* 13:514-522.

Johnsson, J. I. and B. T. Björnsson. 2001. Growth-enhanced fish can be competitive in the wild. *Functional Ecology* 15. In press.

Juskevich, J. C., and C. G. Guyer. 1990. Bovine growth hormone: Human food safety evaluation. *Science* 249:875-884.

Kapuscinski, A. R. and L. D. Jacobson. 1987. *Genetic Guidelines for Fisheries Management*. Duluth, MN: Minnesota Sea Grant.

Kapuscinski, A. R. and E. M. Hallerman. 1990. AFS Position Statement: Transgenic Fishes. *Fisheries* 15(4):2-5.

Kapuscinski, A. R. and E. M. Hallerman 1990a. Transgenic fish and public policy: Anticipating environmental impacts of transgenic fish. *Fisheries* 15(1):2-11.

Kapuscinski, A. R. and E. M. Hallerman 1991. Implications of introduction of transgenic fish into natural ecosystems. *Canadian Journal of Fisheries and Aquatic Sciences* 48 (Suppl. 1):99-107.

Kapuscinski, A. R. and E. M. Hallerman. 1994. *Benefits, Environmental Risks, Social Concerns, and Policy Implications of Biotechnology in Aquaculture*. Contract report prepared for the Office of Technology Assessment, U.S. Congress. Washington, D.C.: National Technical Information Service.

Kapuscinski et al. 1999. Adaptive biosafety assessment and management regimes for aquatic genetically modified organisms in the environment. *Towards policies for conservation and sustainable use of aquatic genetic resources*, edited by R. S. V. Pullin, D. M. Bartley, and J. Kooiman, 225-251. ICLARM Conference Proceedings 59. Makati City, Philippines: International Center for Living Aquatic Resources Management.

Kapuscinski, A. R. 2001. Controversies in designing useful ecological assessments of genetically engineered organisms. In *Genetically Engineered Organisms: Assessing Environmental and Human Health Effects*, edited by D. K. Letourneau and B. E. Burrows, 385-415. Boca Raton, FL: CRC Press.

Kapuscinski, A. R. and D. J. Brister. 2001. Genetic impacts of aquaculture. In *Environmental Impacts of Aquaculture*, edited by K. D. Black, 128-153. Sheffield, UK: Sheffield Academic Press.

Kapuscinski, A. R., L. R. Jacobs, and E. E. Pullins. 2001. Making Safety First a Reality: Final Report of the March 2-3, 2001 Workshop "Safety First: Active Governance of Genetic Engineering for Environment and Human Health Worldwide." St. Paul, MN: Institute for Social, Economic, and Ecological Sustainability, University of Minnesota. Available at www.fw.umn.edu/isees.

Kelso, D. 2000. "Aquarian Transitions: Technological Change, Environmental Uncertainty, and Salmon Production on North America's Pacific Coast." Ph.D. dissertation, University of California, Berkeley.

Kitamura, S., H. Ogata, and H. Onozato. 1991. Triploid male masu salmon Oncorhynchus masu shows normal courtship behavior. *Bulletin of the Japanese Society of Science of Fisheries* 57:2157.

Kitchell, J. F. and S. W. Hewitt. 1987. Forecasting forage demand and yields of sterile Chinook salmon (*Oncorhynchus tshawytscha*) in Lake Michigan. *Canadian Journal of Fisheries and Aquatic Sciences* 44 (Suppl. 5):284-290.

Letourneau, D. K. and B. E. Burrows, eds. 2001. *Genetically Engineered Organisms: Assessing Environmental and Human Health Effects*. Boca Raton, FL: CRC Press.

Lewis, C. 2001. A New Kind of Fish Story: The Coming of Biotech Animals. FDA *Consumer Magazine* January/February. Available at www.fda.gov/fdac/features/2001/101_fish.html.

Li, S. 2001. Professor, Shanghai Fisheries University. Personal communication. November 5.

MacLean, N. and R. J. Laight. 2000. Transgenic fish: an evaluation of benefits and risks. *Fish and Fisheries* 1:146-172.

Marine Stewardship Council. 1998. Principles and Criteria for Sustainable Fishing. Available at www.msc.org.

Marine Stewardship Council. 2001. Marine Stewardship Council Awards Sustainability Label to Alaska Salmon. Available at www.msc.org.

Martínez, R., A. Arenal, M. P. Estrada, F. Herrera, V. Huerta, J. Vázquez, T. Sánchez, and J. de la Fuente. 1999. Mendelian transmission, transgene dosage and growth phenotype in transgenic tilapia (*Oreochromis hornorum*) showing ectopic expression of homologous growth hormone. *Aquaculture* 173:277-283.

Martínez, R., J. Juncal, C. Zaldívar, A. Arenal, I. Guillén, V. Morera, O. Carrillo, M. Estrada, A. Morales, and M.P. Estrada. 2000. Growth efficiency in transgenic tilapia (*Oreochromis sp.*) carrying a single copy of an homologous cDNA growth hormone. *Biochemical and Biophysical Research Communications* 267:466-472.

Matheson, J. February 2000. Questions and Answers About Transgenic Fish. *Information for Consumers.* Rockville, MD: Center for Veterinary Medicine. Available at www.fda.gov / cvm / index / consumer / transgen.htm.

Meffe, G. K. and C. R. Carroll. 1997. Genetics: conservation of diversity within species. In *Principles of Conservation Biology*, edited by G. K. Meffe and C. R. Carroll, 161-201. Sunderland, MA: Sinauer Associates, Inc.

Miller, M. A. and J. Matheson. 1996. Food Safety Evaluation of Transgenic Animals. *FDA Veterinarian Newsletter* Vol. XI. No. II (March / April).

Moriyama, S. 1995. Increased plasma insulin-like growth factor-I (IGF-I) following oral and inter-aperitoneal administration of growth hormone to rainbow trout, *Oncorhynchus mykiss. Growth Regulation* 5:164-167.

Moyle, P. B. and T. Light. 1996. Biological invasions of fresh water: empirical rules and assembly theory. *Biological Conservation* 78:149-161.

Muir, W. M. and R. D. Howard. 1999. Possible ecological risks of transgenic organism release when transgenes affect mating success: sexual selection and the Trojan Gene hypothesis. *Proceedings of the National Academy of Sciences USA* 96:13853-13856.

Muir. W. M. and R. D. Howard. 2001. Fitness components and ecological risk of transgenic release: a model using Japanese medaka (*Oryzias latipes*). *American Naturalist* 158:1-16.

Muir, W. M. and R. D. Howard. 2001a. Methods to Assess Ecological Risks of Transgenic Fish Releases. In *Genetically Engineered Organisms: Assessing Environmental and Human Health Effects,* D. K. Letourneau and B. E. Burrows, 355-383. Boca Raton, FL: CRC Press.

Muir, W. M. and R. D. Howard. 2001b. Assessment of possible ecological risks and hazards of transgenic fish with implications for other sexually reproducing organisms. *Transgenic Research*. In press.

National Agriculture Statistics Service, United States Department of Agriculture. 2000. 1998 *Census of Aquaculture*. Washington, D.C.: National Agriculture Statistics Service. Available at www.nass.usda.gov / census / census97 / aquaculture / general.pdf.

National Institutes of Health. 1986. "Guidelines for research involving recombinant DNA molecules." *Federal Register* 51:16957-16985.

National Institutes of Health. 1987. "Recombinant DNA, notice of advisory committee meeting and proposed actions under guidelines for research." *Federal Register* 52:29800-29814.

National Institutes of Health. 1994. "Guidelines for research involving recombinant DNA molecules." *Federal Register* 59:34496-34547.

National Wildlife Federation. 1996-2002. "Effects of Water Pollution on Human Health." *Saving Our Watersheds program.* Available at http://www.nwf.org/watersheds/human_health.html.

National Research Council. 2002. *Animal biotechnology: Science-based concerns*. National Academy Press. Washington, DC.

Naylor, R. L., R. J. Goldberg, J. H. Primavera, N. Kautsky, M. C. M. Beveridge, J. Clay, C. Folke, J. Lubchenko, H. Mooney and M. Troell. 2000. Effect of aquaculture on world fish supplies. *Nature* 405 (29 June 2000):1017-1024.

Naylor, R. L., R. J. Goldburg, J. Primavera, N. Kautsky, M. C. M. Beveridge, J. Clay, C. Folke, J. Lubchenco, H. Mooney, M. Troell. 2001. Effects of aquaculture on world fish supplies. *Issues in Ecology* (Number 8). Available at http://www.esa.org/issues8.pdf.

Noakes, D. J., R. J. Beamish, and M. L. Kent. 2000. On the decline of Pacific salmon and speculative links to salmon farming in British Columbia. *Aquaculture* 183:363-386.

Nordlee, J. A., S. L. Taylor, J. A. Townsend, L. A. Thomas, and R. K. Bush. 1996. Identification of a Brazil-nut allergen in transgenic soybeans. *The New England Journal of Medicine* 334 (11):688-692.

Office of Science and Technology Policy, Executive Office of the President. 1985. "Coordinated framework for the regulation of biotechnology: establishment of the biotechnology science coordinating committee." *Federal Register* 50:47174-47195.

Office of Science and Technology Policy, Executive Office of the President. 1986. "Coordinated framework for the regulation of biotechnology." *Federal Register* 51:23301-23350.

Office of Science and Technology Policy, Executive Office of the President. 1992. "Exercise of federal oversight within scope of statutory authority: planned introductions of biotechnology products into the environment." *Federal Register* 57:6753.

Office of Technology Assessment, United States Congress. 1995. *Selected Technology Issues in U.S. Aquaculture*. OTA-BP-ENV-171 September 1995. Washington, D.C.: Office of Technology Assessment.

Palmiter, R. D., G. Norstedt, R. E. Gelinas, R. E. Hammer, and R. L. Brinster. 1983. Metallothionein-human GH fusion genes stimulate growth of mice. *Science* 222:809-814.

Parker, I. M., D. Simberloff, W. M. Lonsdale, K. Goodell, M. Wonham, P. M. Kareiva, M. H. Williamson, B.Von Holle, P. B. Moyle, J. E. Byers, and L. Goldwasser. 1999. Impact: toward a framework for understanding the ecological effects of invaders. *Biological Invasions* 1:3-19.

Peacey, J. 2000. The Marine Stewardship Council fisheries certification program: progress and challenges. IIFET 2000 *Conference Proceedings*. International Institute of Fisheries Economics and Trade, Oregon State University, Corvallis. Available at www.orst.edu/Dept/IIFET/2000/papers/peacey.pdf.

Pew Initiative on Food and Biotechnology and The Gene Media Forum. 2001. *The Gene is Out of the Bottle: Where to Next? Public opinion poll about new uses of genetic engineering.* Washington, D.C.: Pew Initiative on Food and Biotechnology. Available at http://pewagbiotech.org/events/0523/0523pollfindings.pdf.

Pew Initiative on Food and Biotechnology 2001a. *Guide to U.S. Regulation of Genetically Modified Food and Agricultural Biotechnology Products.* Washington, D.C.: Pew Initiative on Food and Biotechnology. Available at www.pewagbiotech.org.

Rahman, M. A. and N. MacLean. 1999. Growth performance of transgenic tilapia containing an exogenous piscine growth hormone gene. *Aquaculture* 173:333-346.

Razak, S. A., G-L Hwang, M. A. Rahman, and N. Maclean. 1999. Growth performance and gonadal development of growth enhanced transgenic tilapia *Oreochromis niloticus* (L.) following heath-shocked-induced triploidy. *Marine Biotechnology* 1:533-544.

Riedmiller, S. 1994. Lake Victoria fisheries: the Kenyan reality and environmental implications. *Environmental Biology of Fishes* 39:329-338.

Rodriguez-Clark, K.M. and J.P. Rodriguez. 2001. Beware of trojans bearing fish. *Trends in Ecology and Evolution* 16(8) (August 2001):428.

Scientists' Working Group on Biosafety. 1998. *Manual for Assessing Ecological and Human Health Effects of Genetically Engineered Organisms.* Edmonds, WA: The Edmonds Institute. Available at www.edmonds-institute.org/manual.html.

Status of world aquaculture (1996). 1997. *Aquaculture Magazine Buyer's Guide '97 and Industry Directory* 6-26.

Stern, P.C., and H. V. Fineberg, eds., Committee on Risk Characterization, National Research Council. 1996. *Understanding Risk: Informing Decisions in a Democratic Society*. Washington, D.C.: National Academy Press.

Taylor, M. R. and J. S. Tick. 2001. *The StarLink Case: Issues for the Future*. Report prepared for the Pew Initiative on Food and Biotechnology. Washington, D.C.: Pew Initiative on Food and Biotechnology. Available at http://pewagbiotech.org/research/starlink/starlink.pdf.

Thomson, A. J. 1999. The abundance, distribution and biology of Atlantic salmon in the North Pacific, 1991-1998. 1999 Annual Meeting of the American Fisheries Society, North Pacific- International Chapter, Richmond, British Columbia, March 15-17.

UK Human Genome Mapping Project Resource Centre. Fact Sheet on Tetrodotoxin. Cambridge, UK: The Fugu Genomics Project. Available at http://fugu.hgmp.mrc.ac.uk/PFW/Toxins/tetrodotoxin.html.

Volpe, J. P. 2000. Do we know what we don't know? Atlantic salmon in British Columbia: a review. In *Aquaculture and the Protection of Wild Salmon, Speaking for the Salmon Workshop Proceedings*, edited by P. Gallaugher and C. Orr, 28-33. Continuing Studies in Science at Simon Fraser University, Vancouver, British Columbia. Available at www.sfu.ca/cstudies/science.

Vople, J. P., E. B. Taylor, D. W. Rimmer, and B. W. Glickman. 2000. Evidence of natural reproduction of aquaculture-escaped Atlantic salmon in a coastal British Columbia river. *Conservation Biology* 14(3):899-903.

Wang, R., P. Zhang, and C. L. Hew. 1995. Expression of the antifreeze protein gene in transgenic goldfish (*Carassius auratus*) and its implication in cold adaptation. *Molecular Marine Biology and Biotechnology* 4(1):20-26.

Westlund, Lena. 1995. Apparent Historical Consumption and Future Demand for Fish and Fishery Products – Exploratory Calculations. Kyoto Conference Outcome and Papers Presented. Rome, Italy: Food and Agriculture Organization Fisheries Department. Available at www.fao.org/fi/agreem/Kyoto/H13F.asp#.

Williams, J.D. and G. K. Meffe. 2000. Invasive nonindigenous species: a major threat to freshwater biodiversity. In *Freshwater Ecoregions of North America: A Conservation Assessment*, edited by R.A. Abell et al. Covelo, CA: Island Press.

Youngson, A. F., J. H. Webb, J. C. MacLean, and B. M. Whyte. 1997. Frequency of occurrence of reared Atlantic salmon in Scottish salmon fisheries. *ICES Journal of Marine Science* 54:1216-1220

Zhu, Z. 2001. Professor, Institute of Hydrobiology, Chinese Academy of Sciences, and Member, State Biosafety Committee of China. Personal communication. October 28.