3
Biotechnology

Advances in biotechnology have made the modern aquaculture industry possible. In this report, biotechnology includes traditional technologies, such as hormonally induced spawning, as well as newer techniques including gene transfer and frozen storage of genetic material (cryopreservation) (see table 3-1 and box 3-1).

Early techniques in aquaculture focused simply on collection of organisms, or fertilized eggs from the wild, and transfer to ponds or enclosures of estuarine embay-ments. Production relied on the natural reproduction cycle. Successful fertilization of eggs and spawning of organisms in artificial environments permitted greater con-trol over reproduction. Increased production, and thus large-scale aquaculture, became possible with the discovery of hormonally-induced spawning techniques. Selective breeding and the year-round production of juveniles (and consequently, products), further advanced the industry (30,86).

CONGRESSIONAL INTEREST

Increasing use of biotechnologies in aquaculture is of concern to Congress because federal oversight of some aquatic genetically modified organisms (GMOs) is now fragmented among several federal agencies (table 3-2), while other aquatic GMOs receive no federal oversight. Although several federal agencies have developed guidelines or promulgated regulations governing use of GMOs, some congressional members, scientists and others believe that new legislation, specifically addressing the use and release of aquatic GMOs, may be needed to minimize potential adverse impacts on the environment and human health and safety (74). Congressional interest also focuses on the need for establishing research and funding priorities. Some congressional members as well as scientists and others believe that research

BOX 3-1: Biotechnology Definitions

OTA uses the adjectives **genetically engineered** and **transgenic** to describe plants, animals, and microorganisms modified by the insertion of genes using genetic engineering techniques. **Transgenes** are the genes which are inserted into an organism.

Genetic engineering refers to recently developed techniques through which genes can be isolated in a laboratory, manipulated, and then inserted stably into another organism. Gene insertion can be accomplished mechanically, chemically, or by using biological vectors such as viruses.

Genetically modified organisms have been deliberately modified by the introduction or manipulation of genetic material in their genomes. They include not only organisms modified by genetic engineering, but also those modified by other techniques such as chemical mutagenesis, and manipulation of sets of chromosomes.

Biotechnology refers to the techniques used to make products and extract services from living organisms and their components. A broad interpretation of biotechnology includes all biological technologies important to the successful development of aquaculture, i.e., both traditional technologies such as hormonally induced spawning and selective breeding, as well as newer techniques such as gene transfer and frozen storage of genetic material (cryopreservation). An alternative definition of biotechnology reserves this term for only the newer techniques.

SOURCE: Office of Technology Assessment, U.S. Congress, *Harmful Non-Indigenous Species in the United States*, OTA-F-565 (Washington, DC: U.S. Government Printing Office, September 1993).

TABLE 3-1: Biotechnology Applications and Methodologies

Technology	Description	Species	Potential benefits	Potential risks
Reproduction				
Broodstock maturation	Induced spawning by environmental or hormonal manipulation	Crustaceans, Finfish, Molluscs	Enables year-round production	May require use of unapproved drugs
Induced or synchronized spawning	Hormonal induction of gamete formation	Crustaceans, Finfish, Molluscs	Increases range of species that can be produced	May require use of unapproved drugs
Hybridization between species	Crossbreeding of closely related species	All species	Allows production of offspring with unique characteristicsor sterile organisms	Escapement may cause dilution in wild gene pools
Protoplast fusion	Fusion of plant cells from different species	Aquatic plants	Allows production of offspring with unique characteristics including faster growing varieties	Risks undetermined
Growth and development				
Incubation & larval rearing	Identification of nutritional needs and physical parameters for optimal incubation	All species	Raises productivity, increases growth, and improves survival rates	May pose few risks
Development and metamorphosis	Hastening physical transformation by hormonal or environmental manipulation	Crustaceans, Finfish, Molluscs	Facilitates salt water tolerance in salmon	May require use of unapproved drugs
Growth acceleration & improved food conversion	Administration of hormones	Finfish, Molluscs	Increases growth rate and reduces production time	May require use of unapproved drugs
Sex control/monosex populations				
Direct feminization/ masculinization	Sex change of organism by exposure to estrogen or testosterone derivatives	Finfish	Limits reproduction; creates monosex populations quickly and easily	May require use of unapproved drugs; may not be 100% effective

TABLE 3-1: Biotechnology Applications and Methodologies (cont'd.)				
Technology	**Description**	**Species**	**Potential benefits**	**Potential risks**
Chromosome set manipulation				
Androgenesis Gynogenesis	Production of organisms that contain genetic material from only father or only mother	Finfish	Facilitates production of monosex sperm; enables recovery of organisms from cryopreserved sperm	Escapement may cause inbreeding or gender imbalances in wild receiving populations
Triploidy	Production of organisms with three sets of chromo-somes	Finfish, Molluscs	Retards sexual development, causes sterility; may reduce genetic impact on wild organisms	May cause competition with wild organisms; may not be 100 percent effective[a]
Tetraploidy	Production of organisms with four sets of chromo-somes	Finfish, Molluscs	Facilitates production of triploid offspring	May pose few risks due to low survival in wild
Genetics				
Marker-assisted selection	Introduction of DNA markers into cultured organism	All species	Facilitates traditional selection	May pose few risks
Stock identification with DNA technology	Identification of species and lineage using DNA sequences	All species	Identifies hybrids; separates close relatives for breeding purposes	May pose few risks
Gene banks and sperm cryopreserva-tion	Indefinite storage of genetic material in liquid nitrogen	All species	Allows gene banking for conservation and breeding	May reduce impetus to restore or protect environment
Gene transfer				
Antifreeze gene Nutritional enhancement Disease resistance Growth enhancement	Introduction of a gene that is coded for a specific trait into a new organism	Finfish	Allows expansion of aquaculture to new environments; creates organisms with new traits; speeds up production	May pose ecological, genetic, health, safety and social risks

TABLE 3-1: Biotechnology Applications and Methodologies (cont'd.)				
Technology	**Description**	**Species**	**Potential benefits**	**Potential risks**
Health				
Stress assessment	Investigation of methods to detect and reduce stress	Finfish	Lowers mortality and may increase profits	May pose few risks
Diagnostic tests	Use of sensitive and rapid tests to identify diseases	All species	May increase production and profits	May pose few risks
Vaccine development	Development of vaccines to provide protection against various diseases	Crustaceans, Finfish	May increase production and profits	May pose few risks
Antibiotic development	Development of antibiotics to treat disease outbreaks	Crustaceans, Finfish, Molluscs	May reduce loss to disease	Incurs health and safety and ecological risks
Pharmaceutical delivery mechanisms	Development of methods to deliver pharmaceu-ticals; may be oral, by injection, by immersion, or via implantation	Finfish	May improve efficacy of treatment	May pose few risks
Nutrition	Finding alternative sources of protein and altering diets of cultured organisms	Crustaceans, Finfish	Reduces need for fish protein in diet; may make products healthier for consumers	May pose few risks

NOTE: Amphibians and Reptiles have been excluded from the table

[a] An experiment with transplanted triploid Pacific oysters (*Crassostrea gigas*) was terminated when it was discovered that some of the oysters had reverted to diploid status (see box 3-6) (12).

SOURCES: Office of Technology Assessment, 1995; E.M. Donaldson, Fisheries and Oceans Canada, West Vancouver, British Columbia, "Biotechnology In Aquaculture," unpublished report prepared for the Office of Technology Assessment, U.S. Congress, Washington, DC, November 1994; and A.R. Kapuscinski and E.M. Hallerman, Sea Grant College Program, University of Minnesota, St. Paul, MN, Department of Fisheries and Wildlife Sciences, Virginia Polytechnic Institute and State University, Blacksburg, VA, "Benefits, Environmental Risks, Social Concerns, and Policy Implications of Biotechnology in Aquaculture," unpublished contractor report prepared for the Office of Technology Assessment, U.S. Congress, Washington, DC, October 1994.

TABLE 3-2: Federal Policies and Regulations Related to the Environmental Release of Aquatic Genetically-Modified Organisms Since 1984

Office of Science and Technology Policy	
1992	Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment, 57 *Federal Register* (FR) 6753 (*Policy Statement*)
1990	Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits, 55 FR 31118 (*Proposed Policy*)
1986	Coordinated Framework for Regulation of Biotechnology, 51 FR 23302 (*Policy Statement and Request for Public Comment*)
1985	Coordinated Framework for the Regulation of Biotechnology; Establishment of the Biotechnology Science Coordinating Committee, 50 FR 47174
1984	Proposal for a Coordinated Framework for Regulation of Biotechnology, 49 FR 50856 (*Proposed Policy*)
The President's Council on Competitiveness	
1991	Report on National Biotechnology Policy (*Policy Statement and Recommendations for Implementation*)
U.S. Department of Agriculture, Animal and Plant Health Inspection Service	
1993	Genetically Engineered Organisms and Products; Notification Procedures for the Introduction of Certain Regulated Articles; and Petition for Nonregulated Status, 58 FR 17044 (*Final Rule*)
1992	Genetically Engineered Organisms and Products; Notification Procedures for the Introduction of Certain Regulated Articles; and Petition for Nonregulated Status, 57 FR 53036 (*Proposed Rule*)
1987	Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There Is Reason to Believe Are Plant Pests, 7 CFR 340 (*Final Rule*)
1986	Final Policy Statement for Research and Regulation of Biotechnology Processes and Products, 51 FR 23336 (*Final Policy Statement*)
1986	Plant Pests: Introduction of Organism and Products Altered or Produced Through Genetic Engineering Which are Plant Pests or Which There is Reason to Believe are Plant Pests, 51 FR 23352 (*Proposed Rule and Notice of Public Hearings*)
U.S. Department of Agriculture, Office of Agricultural Biotechnology	
1995	Performance Standards for Safely Conducting Research With Genetically Modified Fish and Shellfish (*Voluntary Performance Standards*)
1990	Proposed USDA Guidelines for Research Involving the Planned Introduction into the Environment of Organisms with Deliberately Modified Hereditary Traits, 56 FR 4134 (*Proposed Voluntary Guidelines*)
1986	Advanced Notice of Proposed USDA Guidelines for Biotechnology Research, 51 FR 13367 (*Notice for Public Comment*)
U.S. Environmental Protection Agency	
1994	Microbial Products of Biotechnology Proposed Regulations Under TSCA, 59 FR 45528 (*Proposed Rule*)
1993	Microbial Pesticides; Experimental Use Permits and Notifications, 58 FR 5878 (*Proposed Rule*)
1989	Biotechnology: Request for Comment on Regulatory Approach, 54 FR 7027 (*Notice*)
1989	Microbial Pesticides; Request for Comment on Regulatory Approach, 54 FR 7026 (*Notice*)
1986	Statement of Policy: Microbial Products Subject to the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act (TSCA), 51 FR 23313 (*Policy Statement*)

SOURCES: Office of Technology Assessment, U.S. Congress, *Harmful Non-Indigenous Species in the United States*, OTA-F-565 (Washington, DC: U.S. Government Printing Office, September 1993); U.S. Department of Agriculture, "1995 Farm Bill--Guidance of the Administration" (Washington, DC, 1995a).

priorities for biotechnologies used in aquaculture should include development of modern technologies as well as applications of traditional methods; and that more emphasis is needed on understanding the consequences of releasing GMOs into the environment, including possible threats to public health or safety (74,139).

ISSUE IDENTIFICATION

Issue: Federal Policy for Biotechnology in Aquaculture

Federal biotechnology policies in the United States are described in the Coordinated Framework for the Regulation of Biotechnology (102,103). Policies described in the Coordinated Framework are based on existing federal legislation to regulate the development and commercialization of GMOs. Existing legislation includes the National Environmental Policy Act (NEPA) (administered by the Environmental Protection Agency) as well as legislation under the jurisdiction of the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) (table 3-2).

The Office of Science and Technology Policy published the "Scope" document in 1992, a supplement to the Coordinated Framework. The Scope document did not change existing regulations but had two prominent features that provided a framework for allowing agencies to exercise discretion in explaining their policies under existing law (25). First, this document declared that regulatory oversight was to be based on characteristics of the organism itself, rather than the process that modified it. Second, regulation of the products of biotechnology would be based on the risks the organism posed to human health or to the environment (74).

The two criteria set forth by the scope document created some controversy. For example, defining a modified organism by its characteristics is difficult. An organism's phenotype or outward appearance is a product of its genetic makeup plus environmental influences, and thus highly variable. Given different environmental influences the phenotype can change. Therefore, each use of a modified organism would have to be evaluated on a case by case basis, which might be impractical when large numbers are involved. Additionally, the uncertain nature of an environmental influence on an organism's phenotype may make it difficult to assess risks that modified organisms could pose in different habitats. Risk assessment and management is currently constrained by a dearth of information needed to assess the release of aquatic GMOs (74).

In recognition of the need to more clearly define how existing laws governed the release of GMOs, several agencies updated their current policies and issued new regulations or guidelines.[1] Publication of the coordinated framework could be considered the start of an ongoing process by which the federal government and agencies explain how biotechnology development and commercialization could be handled (25).

Despite changes in laws and regulations enacted, some believe that regulatory authority over aquatic GMOs may be incomplete. For example, National Institutes of Health (NIH) guidelines for research with recombinant DNA do not necessarily apply to aquatic GMOs and use of the NIH guidelines may be voluntary in certain circumstances[2] (74,95,96,97). In addition, it may be difficult to determine which agency has jurisdiction over the regulation of an aquatic GMO (box 3-2.). For example, APHIS regulates release of certain genetically modified plants and live animal vaccines and EPA regulates the release of some genetically modified microbes and has proposed legislation to regulate microbial products of biotechnology and plants containing pesticide genes (51,139).

---

[1] For example, USDA's Animal and Plant Health Inspection Service (APHIS) promulgated new regulations in 1987 under the Federal Plant Pest Act and the Plant Quarantine Act and added amendments to these regulations in 1993 (74). FDA issued a policy statement clarifying its interpretation of the Federal Food, Drug and Cosmetic Act with respect to foods derived from new plant varieties and issued guidance for safety evaluation.

[2] Federal agencies or organizations that receive federal dollars or use federal resources are required to comply with NIH guidelines. Private sector activities without federal involvement are not required to comply with NIH guidelines but often do so voluntarily (25).

However, many genetically modified aquatic organisms do not clearly fall under the umbrella of any legislation when they are conducted by the private sector. Some have suggested the Lacey Act be invoked to regulate "unassigned" GMOs but this legislation delegates responsibility for oversight of releases of fish and game to the states. State legislation may not be as desirable because aquaculture products may be regulated more effectively under a federal framework that simplifies commerce among companies in different states, and state oversight may not adequately protect the environment because many states lack oversight programs for GMOs (51). Another alternative is for the FWS to become involved in limiting interstate transport of species designated as prohibited or injurious by a state (139). FWS already provides certification services to ensure that grass carp (*Ctenopharyngodon idella*) are triploid (139).

FDA also may have a role to play. The definition of a new animal drug (chapter 2) is broad enough to include the introduction of transgenes into an organism. If FDA declared that transgenes were new animal drugs then they would have the authority to regulate all stages of commercialization of transgenic organisms including the investi-gational or developmental stages prior to production. This approach may hinder commercial production of transgenic aquatic organisms because of the high costs associated with obtaining new animal drug approvals (25,68).

Anticipating further requests for releases, the USDA Office of Agricultural Biotechnology, through a working group under its Agricultural Biotechnology Research Advisory Committee (ABRAC), developed Performance Standards for Safely Conducting Research with Genetically Modified Finfish and Shellfish (2). The

BOX 3-2: Release and Confinement of Transgenic Fish

To date, only two federally-funded outdoor experiments with transgenic aquatic organisms have taken place in the United States. In both cases, the USDA Cooperative State Research, Education and Extension Service (CSREES)[a] requested the Agricultural Biotechnology Research Advisory Committee (ABRAC) to provide assistance in the environmental assessment. The first study, proposed for confined outdoor ponds by Auburn University's Agricultural Experiment Station, involved rearing a transgenic line of common carp (*Cyprinus carpio*) with a rainbow trout growth hormone gene (74).

Initially there was some confusion about which Federal agency claimed jurisdiction over the project and the appropriate Federal forum for review of the proposal's safety.[b] Eventually it was determined that the responsibility for oversight of the experiment lay with the agency partially funding the research, in this case CSREES (139). Under the National Environmental Policy Act (NEPA), an environmental assessment was conducted by CSREES and no significant environmental impact was found associated with the project. This finding was met with strong criticism and prompted the agency to conduct another assessment with help from ABRAC. The new assessment also concluded that the experiment would result in no significant impact to the environment but was contingent upon significant improvements to the outdoor facilities at Auburn University. Modifications included rearing fish in ponds at a higher elevation (to avoid the floodplain) and effluent filtration (139).

In 1992, Auburn University subsequently sought approval to use federal funds to conduct a similar study with transgenic channel catfish (*Ictalurus punctatus*) in newly constructed ponds above the 100-year flood plain and built with numerous barriers to escape including several barriers in effluent filtration (75). The study was approved after CSREES analyzed the data and determined that the experiment would have no significant impact. In both cases, the reviews were conducted without benefit of guidelines tailored to issues raised by aquatic GMOs, which led the ABRAC to develop guidelines (2,74).

[a] Formerly the Cooperative State Research Service (CSRS).
[b] When a regulatory agency has jurisdiction over an activity funded by another agency, normally the regulatory agency (sometimes in collaboration with the funding agency) conducts the environmental review consistent with NEPA (25).
SOURCE: Office of Technology Assessment, 1995.

Performance Standards are a focused step toward defining clear U.S. oversight policy on the development and use of genetically modified aquatic organisms. The Performance Standards are voluntary guidelines for assessing the environmental effects of proposed research with genetically modified fish and shellfish, excluding organisms modified solely by traditional breeding, and, when use of the standards leads to identification of specific risks, for selecting confinement measures (74). These guidelines establish a methodology for assessing which organisms present problems to wild organisms and natural ecosystems (boxes 3-3 and 3-4). The guidelines also provide risk management recommendations and recom-mend peer review of proposed projects and evaluation of the facilities used in the experiment (2).

Environmental reviews of the release of aquatic GMOs under federally-funded research programs are also carried out by funding agencies in accordance with their obligations under the National Environmental Policy Act (NEPA). NEPA requires all federal agencies to consider the environmental consequences of actions, including a decision to fund a particular research study. Although NEPA requires full consideration of environmental consequences, it does not preclude approval of actions even when they may have a significant impact (74).

The Food and Drug Administration (FDA) is one of the agencies with jurisdiction over products of biotechnology. FDA regulates new animal drugs under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b). Drugs are defined in this Act as articles other than food intended for use in the diagnosis, treatment, or prevention of disease, or that affect the structure or function of the body of an animal. Although FDA policy in this area is still under development, the agency may find that introduction of transgenes[3] intended to affect the structure or function of an animal's body constitutes a new animal drug use. If FDA decides to take this approach, the agency would have the authority to approve commercialization of transgenic fin-fish or shellfish, provided that the transgenes (the "new animal drug") were determined to be safe for the animal and for persons eating foods derived from the animal (74,130). Under NEPA, FDA would also have to fully consider the environmental impacts of transgenic finfish and shellfish before they were approved by the agency (51).

BOX 3-3: Frequency of Escape from Aquaculture Facilities

What is the chance that organisms will escape from aquaculture facilities or be released into the environment as a result of aquaculture activities? This question is an important one to consider when assessing environmental risks. In the past, large numbers of organisms are thought to have escaped from aquaculture facilities, especially from ocean net pens used to raise finfish. For example, in 1993 the Canadian Department of Fisheries and Oceans reported that 4,500 farmed Atlantic salmon had been captured from the Pacific coast and that total estimated catch was probably closer to 10,000 farmed fish. Similarly, 32,000 fish reportedly escaped in 1994 from one aquaculture facility in British Columbia.

Fish aren't the only organisms that can escape or be released into the environment as a result of aquaculture activities. Pacific white shrimp (*Penaeus vannamei*) have been captured off the coast of South Carolina (139). Aquatic plants used in the aquarium trade, such as hydrilla and water hyacinth, were introduced into canals in Florida and have subsequently become plant pests (72,139). Likewise, potential establishment of the Pacific Oyster (*Crassostrea gigas*) in the Chesapeake Bay was narrowly averted when an experiment with triploid oysters failed. In this incident, a percentage of triploid oysters reverted into diploid organisms capable of reproduction (box 3-6) (12) but were removed from the bay before spawning occurred.

SOURCE: Office of Technology Assessment, 1995.

---

[3] Genes coding for specific traits isolated from one organism, copied, and transferred to another organism.

BOX 3-4: Assessing Environmental Risks of Aquatic Genetically-Modified Organisms

Risk assessment is a systematic process used to identify risks posed by certain activities to human health or to the environment. Risks are then evaluated and compared to benefits of the same activities. Results of the evaluation subsequently are used to develop public policy. Some analysts describe risk assessment as a method that connects science to policymaking (100).

The risk assessment process has been used widely in determining risks of activities to public health. For example, exposure to specific chemicals at known concentrations over a certain period of time may cause illness. Information from previous exposures can be used to estimate "safe" levels of exposure and thus assist in creation of public policy.

In 1993, the National Research Council presented a framework to adapt the risk assessment process to ecological risks (100).[a] The Council defined ecological risk assessment as "the characterization of adverse ecological effects of environmental exposures to hazards imposed by human activities." Five components contribute to the ecological risk assessment process:

- *Hazard identification*: The determination of whether a particular agent poses health or environmental risks sufficient to warrant further scientific study or immediate management action.
- *Exposure-response assessment*: Evaluation of the link between the magnitude of exposure and the probability that the potential effects will occur. For example, if a large number of sterile triploid organisms escape from an aquaculture facility, there may be a high probability of competitive interaction with native organisms but low incidence of reproductive activity.
- *Exposure assessment*: Determination of the extent of exposure before or after regulatory controls. Exposure can include nonchemical stresses such as the introduction of a new species.
- *Risk characterization*: Description of the nature and magnitude of the risk, including uncertainty, presented in a way that is understandable to policymakers and the public.
- *Risk management*: Formulation of public policy to manage risks and balance societal needs using information generated from the previous steps.

This framework might be used to assess ecological risks posed by using genetically modified organisms (GMOs) in aquaculture and to develop appropriate policy regulating their use. Several problems exist, however, in applying this framework generally to decisions about the management of natural resources and, specifically, to aquatic GMO regulation and decisionmaking.

Politicians, regulators, scientists, and private property owners debate the need for and effectiveness of using risk assessment and its integral valuation and cost benefit analyses as a touchstone for environmental policy. Proponents of risk-assessment procedures for evaluating development and regulatory decisions typically hail the structure and uniformity it affords to contentious issues. Opponents claim that economics as a driving decision-making tool downplays the importance of aesthetic, moral, cultural, and historical values that require the preservation of nature (122).

Although methods have been developed for assigning dollar amounts to ecological values, uncertainties associated with their application remain high (100,122). It generally has been easier to develop techniques to determine economic values for resource "use" values (such as boating and hunting), than for resource "nonuse" values (such as spiritual appreciation or preserving a legacy for future generations). Assigning economic values to nonuse values requires subjective evaluation and results are variable depending on the evaluator's geographic location, employment, and education, as well as assessment method.

Lack of information and lack of a track record with newly developed methodologies (2) make it especially difficult to assign values to risks posed by aquatic GMOs. Each aquatic GMO has specific traits affecting its persistence, competitiveness, and adaptability in natural ecosystems (74). Adverse genetic and ecological effects of released aquatic GMOs will depend on characteristics such as the nature and degree of change in the physical characters and performance of the GMO; potential for the GMO to disperse, reproduce, and interbreed; and the GMO's potential for adaptive evolution. Uncertainties in behavior of aquatic GMOs make it problematic to accurately predict long-term environmental consequences of releasing them into an ecosystem. Thus, the absence of previous experience with and population records for aquatic GMOs may continue to make them difficult candidates for the ecological risk assessment process.

[a] The 1993 framework was redesigned from an earlier, more generalized version: National Research Council 1983, Risk Assessment in the Federal Government: Managing the Process (the "Red Book").
SOURCE: Office of Technology Assessment, 1995.

Agencies responsible for overseeing environmental release of aquatic GMOs include the U.S. Fish and Wildlife Service (FWS), National Marine Fisheries Service (NMFS), and various state agencies overseeing aquatic resources. FWS and NMFS have mandates to protect the genetic integrity of wild stocks, aquatic habitat, and biological diversity. For example, under the Lacey Act, the FWS has authority to control impacts from migratory species, exotic species, or any aquatic species that cross state lines. Likewise, if the release of aquatic GMOs is likely to have an impact on threatened or endangered species, the FWS or NMFS will have responsibility to oversee these activities under the Endangered Species Act (ESA). The FWS and NMFS, however, lack specific mandates for regulating development and production of aquatic GMOs (74).

Because federal agencies have restricted jurisdiction over state waters, certain states have created their own laws regulating the release of GMOs into the environment (139). Certain of these regulations go beyond the provisions of the Coordinated Framework and subsequent federal regulations to address key loopholes or procedural ambiguities (74). Most of the state regulations, however, are aimed at GMOs in general rather than aquatic GMOs specifically (North Carolina Gen. Stat. §106-772 (1994);[4] Minnesota Statutes Chapter 116C.91-.98, as amended by 1994 Session Law, Chapter 454).

Aquatic organisms pose additional problems for regulation because they may cross national boundaries. Therefore, international policies governing the release of aquatic GMOs also are necessary. Agencies such as the Organization for Economic Cooperation and Development (OECD), the International Council for Exploration of the Seas (ICES) and the Food and Agriculture Organization of the United Nations (FAO) have investigated policy issues raised by the release of aquatic GMOs (74).

Recent examples of international collaboration for forming policy to govern the release of aquatic GMOs include an ICES Code of Practice, an FAO Review of Biotechnology in Aquaculture, and a workshop sponsored by the OECD held in June 1993 entitled "Environmental Impacts of Aquaculture Using Aquatic Organisms Derived Through Modern Biotechnology" (105). Amendments to the ICES Code of Practice in 1990 address concerns raised by aquatic GMOs (27). The amendments call for: any person or organization involved in "genetically modifying, importing, using or releasing any genetically modified organism" to obtain a license; risk assessment to determine the potential effects aquatic GMO release could have on the environment; initial release of GMOs to be performed with reproductively sterile organisms to reduce potential genetic impacts on the receiving population; and more research on ecological effects modified organisms may have in the environment (27).

Issue: Consequences of Releasing Aquatic GMOs into the Environment

Undesirable changes in wild gene pools may occur if cultured organisms interbreed with wild individuals. Wild-type genes could be replaced by the introduction of new genes from the cultured organisms, resulting in a loss of natural genetic variation (box 3-5) (117). Loss of genetic variability in wild populations also could restrict future options for hatchery programs and aquaculture breeders. Then, breeders relying on wild genetic material to increase genetic diversity in their captive broodstocks may be unable to

[4] This law has a "sunset" provision that automatically repeals the legislation on September 30, 1995, if the North Carolina legislature does not renew it (51).

find sufficient variety of wild genetic material (74,126).

Another undesirable change caused by cultured organisms interbreeding with wild individuals is the introduction of deleterious genes into a wild population. Wild organisms are specifically adapted to the ecosystem they inhabit. Genes and gene combinations in wild populations may determine coloration, swimming stamina, disease resistance, and other qualities necessary for survival (64). Genetic traits useful for cultured species, such as docility and rapid growth, may not be beneficial for survival in the wild. Thus, reproductive success of escaped farmed fish and of hybrid offspring produced from cultured fish interbreeding with wild fish may be considerably less than reproductive success of wild fish (box 3-5) (109,118).

BOX 3-5. Genetic Dilution by Introgressive Hybridization

Striped bass (*Morone saxatilis*) (also known as Rockfish in the Chesapeake Bay) is a popular game and food fish, native to many Atlantic coastal states. Hybrid striped bass are produced by crossing striped bass with white bass (*Morone chrysops*). The hybrid offspring are fertile and can mate with either parental species or other hybrids. Interbreeding of hybrid striped bass and indigenous striped bass has been documented in areas where these fish coexist (26,42,60).

Stocking of hybrids for sport fishing was widespread in the Chesapeake Bay area in the 1980s. At one time it was estimated that hybrid bass may have comprised as much as 20 percent of the total winter population of striped bass in the Maryland segments of the bay (60).

Striped bass native to the Chesapeake Bay are uniquely suited to their environment. One special adaptation is the production of floating eggs that are able to withstand frequent tidal changes. The eggs remain suspended in the water column instead of sinking to the bottom where they could be covered with silt and destroyed (76). Striped bass from other areas outside of the bay and hybrid striped bass do not share this unique characteristic (116).

Bass lacking the ability to produce floating eggs may not exhibit high reproductive rates in the Chesapeake Bay ecosystem. Therefore, large numbers of hybrid striped bass, interbreeding with native striped bass could result in lower reproductive success and potentially lead to severe population declines in the native striped bass (60).

SOURCE: Office of Technology Assessment, 1995.

Cultured organisms may cause undesirable changes in wild populations by upsetting gender balances as has been observed in some hatcheries (126). It is often advan-tageous to culture monosex populations because one sex may exhibit superior qualities such as faster growth rates (31). A large number of either male or female organisms released into the environment, produced by technologies such as direct feminization or masculinization, might produce skewed populations after mating. Subsequent population sizes could be reduced by inbreeding caused by distorted sex ratios (126). This may be of particular concern for some species, such as some salmonids, that spawn once and die.

Techniques to induce sterility are not always effective. Producing organisms with three sets of chromosomes (triploid organisms) sometimes is not 100 percent successful (box 3-6). In some bivalves, the percentage of triploid individuals ranged from 63.4 to 88.4 using various techniques (124). In finfish, pressure and temperature shocks can be 94 to 100 percent efficient in inducing triploidy (technique used to produce sterile organisms) (85,94). Incomplete triploid induction may lead to the inadvertent release of fertile individuals that subsequently interact with wild species or establish new breeding populations of non-indigenous species (74).

Even when sterility induction is successful, some triploid organisms may engage in reproductive behavior. If sterile organisms attempt to spawn, they may prevent members of the wild population from fertilizing eggs. Additionally, if these organisms produce sperm they could "fertilize" normal eggs rendering them inviable (32). Large numbers of sterile individuals attempting to spawn could cause natural populations to decline (74).

Certain genetically modified organisms introduced into natural environments may also interfere with ecosystem functioning by altering important species interactions. For example, fish with introduced growth hormone genes may have higher metabolic rates and attain larger sizes at a given age than wild fish. The larger fish might then out-compete smaller, unaltered fish for food, habitat resources, or spawning sites (74). Additionally, faster growing fish may have larger mouth gapes enabling them to use new prey species or consume larger size classes of traditional prey species (56,73). Genes that extend tolerances of physical factors also might permit altered species to extend their geographical range and destabilize new ecosystems (74).

BOX 3-6: Is Induced Triploidy Reversible?

In June 1993, experiments were conducted on introduced triploid Japanese Oysters (*Crassostrea gigas*) in the York River, Virginia, a section of the Chesapeake Bay (154). Each oyster was tested to ensure triploidy before placing it in the river. After four months, one of the oysters was found to be diploid and thus capable of reproducing. Follow-up examinations revealed that many other oysters (20 percent) had become diploid or were mosaics of triploid and diploid cells (indicating partial reversal). An evaluation of the process used to create the triploid organisms showed that the procedures had been followed correctly. The triploid oysters had reverted by progressively replacing triploid cells with diploid cells.

The experimental introduction into the wild was halted when it was found that these organisms were capable of reproduction. Although reproduction could have taken place, cold water temperatures are believed to have prevented the introduced organisms from reproducing in the Chesapeake Bay (12).

The incident described above, though unprecedented, raises the question of reversible triploidy in other organisms. Triploid grass carp, tilapia, and rainbow trout have been introduced into aquatic habitats or raised in aquaculture for some time. What is the potential for these organisms to revert to the diploid state and reproduce? More research is needed to answer these questions and to prevent potential problems.[a]

[a] In 1995, the Biological Risk Assessment Research Grants Program (administered by the National Biological Impact Assessment Program) awarded $160,000 to the Haskin Shellfish Research Laboratory to investigate this problem. A study, entitled "Triploids for Biological Containment: The Risk of Heteroploid Mosaics," will take two years to complete.
SOURCE: Office of Technology Assessment, 1995.

Issue: Consumer Health and Safety Concerns

Human health could be affected by the use of biotechnologies if food derived from these organisms contains harmful substances. There are concerns that biotechnology proce-dures, such as gene transfer, could cause an organism to produce higher levels of existing toxins, novel toxins, or to become resistant to naturally occurring toxins and thus accumulate high levels in their tissues (74).

Toxins in commonly consumed fish and shellfish have been shown to come from external sources. Some scientists, therefore, have argued that transgenic fish and shellfish are generally unlikely to produce novel toxins (8,104). And, although some aquatic plants do produce toxic substances, several arguments suggest that current gene transfer techniques have a low likelihood of stimulating the production of new toxins. First, the production of toxins usually is a complex process that involves several steps. Transfer of one or a few genes into an algael species that does not normally produce toxins is unlikely to initiate production of new toxins. Second, knowledge about the production of toxins and their distribution in marine algae is extensive. The availability of this information could make it possible to predict which species might produce new toxins. Transgenic aquatic plants capable of producing toxic substances could be screened for the presence of harmful products prior to permitting their commercial culture (74).

Allergens present a second health and safety concern related to use of biotechnology in aquaculture. Foods derived from transgenic fish, shellfish, or aquatic plants could contain proteins not normally found in the parent species or proteins produced at higher-than-normal levels. Some of the introduced or higher-than-normal levels of proteins could cause allergic reactions in susceptible consumers (52).

BOX 3-7: Religious and Ethical Concerns

Opposition to the use of biotechnology in aquaculture may arise from strongly held religious or ethical beliefs. Some groups believe that it is immoral to tamper with the sanctity of life. Transferring genes from one organism to another may be equated to "playing God" or "interfering with nature." Other religions hold that all life forms have been created in the best form and that organisms should not be altered by humans except to return deviations to their original form (23).

The nature of the transferred gene also may cause concern among specific interest groups. The transfer of genes of human origin into an organism used for consumption by humans might be unacceptable to some people. Some religions believe that a gene retains the essence of its original host. Thus, consuming an organism containing a copy of a human gene would be forbidden on religious grounds (23).

Other groups may be concerned that genes from animals whose flesh is forbidden for consumption may be present in organisms grown for food. This group could include vegetarians who may not want to eat plant materials that contain genetic information from animals (23).

Some animal rights' activists may object to technology they perceive to cause suffering in cultured species. For example, in an experiment to produce animals with leaner meat, pigs were injected with the human growth-hormone gene (51). The transgenic pigs attained leaner meat but also became arthritic. Animal rights' groups protested the use of this technology due to the suffering of the pigs (23).

It is possible that similar situations could arise in the aquaculture industry. For example, in an experiment with transgenic sockeye salmon (*Oncorhynchus nerka*), an introduced growth-hormone gene produced rapid growth that led to skeletal deformities (74). The observation of deformities in the fish might lead people to conclude that the fish had suffered as a consequence of the procedure and could result in protests.

Increased use of gene transfer technologies in aquaculture may bring religious and ethical concerns to the forefront. Several solutions have been proposed to address these concerns. First, attempts could be made to find gene donor sources from closely related species and not from controversial sources such as humans or consumption-restricted organisms. Second, foods that contain gene products from culturally-prohibited sources (e.g., products derived from pigs or animal flesh) could be labeled accordingly. And third, educating consumers about the biotechnology methods used to produce the organisms might help to reduce public concern over consumption of these substances. Consumers, for example, might be informed that the DNA used in a particular process was synthesized in a laboratory rather than removed from an animal (23).

SOURCE: Office of Technology Assessment, 1995.

Correct identification of aquatic GMOs that might elicit food allergies is difficult because of an inadequate database and lack of conclusive information on the allergenicity of introduced proteins (59,74). Comprehensive screening methods for predicting which foods derived from aquatic GMOs could elicit allergic reactions require further investigation (74). To date, however, presence of a food allergen has not been a basis for keeping a product off the market.[5] Consumers generally rely on food labels to avoid consuming known allergens (74). Avoidance of allergens in

[5] Pioneer HiBred, a company that develops and markets seeds, ceased research on commercializing genetically-engineered soybeans when studies showed that the soybeans elicited allergic responses in some consumers (50).

foods derived from transgenic fish or shellfish would therefore require that these foods be labeled as such. The FDA has not yet issued a decision on this issue (51,75).

Issue: Patenting of Aquatic GMOs

In a series of decisions in the 1980s, the Supreme Court ruled that genetically manipulated microorganisms, plants, and multicellular animals could be patented (29,38,37, 74). To date, four transgenic mice have been patented in the United States (17,54) and at least 180 animal patents are pending (4).

Patenting life generates many legal questions as well as religious and ethical concerns (box 3-7). For example: What do patents cover--one organism or a technique? What are the provisions for royalties? How are patents to be issued? How is proprietary protection granted? These questions are beyond the scope of this report but are discussed in detail in the Office of Technology Assessment Special Report "New Developments in Biotechnology: Patenting Life" (138).

Some biotechnology applications in aquaculture, such as gene transfer or chromosome set manipulation, may lead to future attempts to patent modified organisms. Patenting aquatic GMOs could be beneficial to the aquaculture industry in several ways. Patents for GMOs might provide economic incentives through royalties to inventors for development of genetically modified lines of cultured organisms. Patents for GMOs also might facilitate technology transfer through full disclosure requirements of techniques used to modify the organism in the patent application (74,78).

Conversely, patenting aquatic GMOs could harm the aquaculture industry. Patent holders could charge prohibitively large royalties for original broodstock effectively limiting entry to larger operations. Broad patents granted for an entire species could limit research, testing, and commercialization of aquatic GMOs (54,74). Additionally, opponents of patenting life forms argue that patenting life might lead to suffering of transgenic animals and reflect an inappropriate sense of human control over animal life (box 3-7) (74,138).

Issue: Use of Biotechnologies and Attitudes toward Environmental Protection

Some believe that extensive use of these technologies may lead to a society opting for changing organisms rather than preserving, protecting, or restoring the environment. Technologies such as gene transfer and chromosome set manipulation can alter organisms in such a way that they can tolerate degraded environments. Altered traits may allow GMOs to survive in impaired environments. For example, acid resistant hybrid brook trout have been developed for stocking in Adirondack lakes affected by acid rain (122). Similarly, the "saugeye" (a cross between a walleye and a sauger) lives in polluted waters where walleye cannot survive (122). Such technologies could influence society to respond to environmental degradation not by addressing the reasons for the impairment but rather by altering managed species to accommodate new conditions (74,122,139). Genetic modification, therefore, poses questions about our societal values and the management of aquatic ecosystems.

A similar concern is that emphasis on aquatic GMOs, highly tailored to human desires, will encourage our society to abandon efforts to rebuild and sustain natural fish stocks and the ecosystems on which they depend. In contrast, however, it is also argued that higher production rates in aquaculture made possible by new biotechnologies could help to reduce fishing pressure on wild stocks.

Issue: Research and Funding Priorities for Biotechnologies Used in Aquaculture

The potential of some modified organisms to have unintended effects on the environment and consumer health and safety has led to debates on research and funding priorities for biotechnologies used in aquaculture. Research on biotechnology has focused traditionally on development of methods and the benefits of their application. Little research has evaluated the potential impacts that modified organisms may have on the environment. The National Biological Impact Assessment Program (NBIAP), managed by USDA, is one federal research grant program designed to investigate concerns regarding environmental effects of biotechnology. Funding for this program, which evaluates the potential risks of biotechnology research conducted by the Department of Agriculture, has been criticized as inadequate (74).[6]

Additional criticism of current funding priorities in aquatic biotechnology is directed towards choice of technologies investigated. Past research funding is criticized for emphasizing newer, more glamorous technologies, possibly at the expense of older proven technologies. For example, traditional selective breeding has been highly successful in aquacultural contexts but some argue that it is not used widely enough. Research funding, generally allocated in short segments (typically two years), also discourages research on selective breeding due to time constraints. A fragmented aquaculture industry largely composed of small producers with few resources cannot afford to initiate long-term breeding programs. Thus, most research on selective breeding has to be carried out by governments and, to some extent, universities. A few federal laboratories are engaged in traditional breeding activities, but studies seem to focus on only a few major species and a few traits (74).

BIOTECHNOLOGY APPLICATIONS AND BENEFITS

Many biotechnologies used in aquaculture are developed to increase production, reduce costs of production, manage disease outbreaks, raise the value of currently cultured organisms, or result in the culture of new species (table 3-1). Several biotechnologies, including gene transfer and selective breeding, focus on reducing the amount of time needed to bring a product to market. Long production cycles often distinguish aquaculture from traditional land-based agriculture. Terrestrial livestock, such as poultry or cattle, have production cycles measured in weeks or months while production of aquaculture products may be measured in years (most cold water species such as salmon may grow to a marketable size after two to three years) (31). The transfer of growth hormone genes into coho salmon produced transgenic fish that on average were 11 times heavier than non-transgenic controls (28) (box 3-8). Traditional breeding also has been effective. Coho salmon (*Oncorhynchus kisutch*) selected for rapid growth over four generations were 60 percent heavier after eight months of salt water grow-out than fish at the same stage in the first generation (31,63). Combining selective breeding with marker-assisted selection (identifying specific sequences of DNA associated with desirable traits) could also increase growth rates. DNA marking or introduction of known DNA segments could be used for tracking purposes.

Higher production rates also may result from using technologies to modify organisms so they can tolerate new environments (box 3-8). In some instances, hybridization has been used to produce organisms more tolerant of adverse conditions than either parent species (122). Likewise, gene transfer has the potential to affect the ability of an organism to live in a different environment. For example, transfer of a gene that encodes an "antifreeze protein" from winter flounder (*Pseudopleuronectes americanus*) to Atlantic salmon (*Salmo salar*) (41) (box 3-8) may increase the salmon's tolerance to freezing conditions, leading to increased salmon production in northerly regions.

Raising organisms in high densities can lead to mortality from stress and subsequent disease outbreaks. Various biotechnologies,

[6] Funding for this program was approximately $1.7 million for fiscal year 1994 (49).

such as new vaccines, are aimed at reducing disease outbreaks. Quick and accurate methods for diagnosing disease outbreaks could help to ensure rapid treatment before organisms suffer significant mortality. Gene transfer, marker-assisted selection, as well as selective breeding for low response to stress offer the possibility of producing organisms better able to resist diseases (31,40,74).

Several biotechnologies offer ways of increasing the value of aquacultural products. Aquaculturists already use these techniques. For example, production of monosex female salmonids allows salmon farmers to produce fish that mature later and grow to larger sizes than male salmonids. Larger salmonids bring in higher prices at the market. Monosex female rainbow trout are cultured widely in North America for this reason (31). Likewise, triploidy, a technique used to produce sterile organisms, is used to culture rainbow trout and Atlantic salmon on a commercial scale in North America and Europe. Triploid Pacific oysters (*Crassostrea gigas*) are produced to suppress reproductive maturation leading to oysters with higher meat quality during summer months (3). Strategies that improve the nutrition of the marketed product such as a lower fat diet of the cultured organism also can raise the product's value by making it more desirable to the consumer. Likewise, selective breeding experiments over three generations have produced catfish with 29 percent higher body weights and higher percentages of edible body tissue (35).

Biotechnologies can facilitate culture of new species. New species must be marketable and amenable to culture from an early life stage to market size in captivity (31). Biotechnologies that increase the economic benefits of aquaculture production are important as well as to the development of a new culture species. For example, producers

BOX 3-8: Potential Benefits of Gene Transfer

Gene transfer technologies, or the ability to transfer desirable traits from one organism to another, may hold great promise for aquaculture producers. Gene transfer might be used to enhance natural growth or modify environmental tolerance of cultured aquatic organisms.

Previous attempts at raising levels of growth hormone by injection in fish were time consuming and impractical to implement on a large scale. Recent experiments may lead to a more efficient method of introducing hormones from one aquatic organism to another. Fertilized eggs from coho salmon were injected with a growth hormone gene derived from sockeye salmon (28). After 14 months of growth, the transgenic salmon were on average more than 11 times heavier than untreated controls. The largest fish was 37 times heavier than the average controls (28). The transgenic salmon also exhibited the silver coloration characteristic of more mature fish physically ready to begin the migration from freshwater to saltwater (28).

Results from this experiment may eventually lead to products ready for market sooner leading to higher profits for producers. Increasing the rate at which the physical transformation needed for saltwater growout occurs could simplify the culture process as well as reduce high costs associated with raising young fish in a hatchery for extended periods.

Environmental tolerance is another production characteristic that may be amenable to alteration by gene transfer. Some fish, for example the winter flounder (*Pseudopleuronectus americanus*), can survive in "supercooled" seawater because they have specific proteins which prevent their blood from freezing (41). These proteins prevent ice crystal formation in a manner similar to the way antifreeze prevents water in a radiator from freezing.

Salmon lack antifreeze proteins and, thus, water in the blood can freeze at temperatures below -0.7º C (30.7º F)(freshwater freezes at 0º C or 32º F), resulting in mortality (74). The transfer of the gene coding for antifreeze protein from winter flounder to Atlantic salmon therefore may be able to extend the northern range for net pen salmon farming. To date, researchers have transferred the antifreeze gene to salmon, but, the protein is not yet produced at high enough levels to confer significant freeze resistance to the fish (31,41).

SOURCE: Office of Technology Assessment, 1995.

of each newly cultured species can take advantage of technologies that increase production to meet market requirements, treat diseases particular to the species, and provide nutritionally complete and economic diets for each life history stage (31).

Use of biotechnology in aquaculture has environmental and social consequences as well as economic ones. First, wild fish stocks may be affected by interbreeding with escaped fertile organisms or by new competition from self-sustaining populations of non-indigenous species. Using sterile triploid organisms such as grass carp (*Ctenopharyngodon idella*), could reduce possibilities for this non-indigenous species to increase its abundance and displace other native species when released in the wild (74). In the future biotechnology techniques may create organisms incapable of surviving in the wild after escape (similar to domestic chickens or cattle), therefore reducing environmental impacts (51). Second, juveniles of some species raised worldwide such as shrimp, milkfish (Chanos chanos) and eels (Anguilla spp.) are collected from the wild due to an inability to cost-effectively complete their life cycles in captivity. Information on the life cycles of these organisms would be useful for developing practical spawning techniques that could reduce the collection of juveniles from the wild (31). Third, developing feeds using complete proteins derived from enhanced plant sources instead of fish meal could help to reduce the overharvest of organisms used to manufacture fish meal. Fourth, biotechnologies that lead to higher production rates or more desirable products might reduce pressures on wild stocks.

In addition to protecting wild stocks by reducing harvesting pressures, biotechnologies such as cryopreservation (storage of genetic material in liquid nitrogen) offer the potential to preserve unique genetic resources. In emergency situations, when local stocks or entire species face extinction, cryopreservation can be used to store genetic material from these organisms. For example, sperm from the endangered Redfish Lake sockeye salmon (*Oncorhynchus nerka*) has been collected and stored using this technique (134). A drawback of relying only on cryopreservation to conserve genetic resources is that it arrests the ongoing evolutionary adaptation of living organisms to their constantly changing environments, a process which is essential for long-term persistence of a species (74).

Biotechnological applications in aquaculture products may also protect the consumer. Breeding disease-resistant organisms, transferring genes for disease-resistance, and using vaccines can reduce disease outbreaks. Timely diagnosis of disease could reduce the need for emergency use of antibiotics or other chemicals (31). Reduced use of antibiotics may address concerns about formation of antibiotic-resistant bacteria potentially causing disease problems in wild and cultured species or humans, and the possibility of residues of these substances showing up in food products (10,36,90).

CONCLUDING REMARKS

Biotechnology plays an important role in the development of aquaculture. Biotechnologies are used to induce reproduction; hasten growth and development; produce monosex populations; alter other performance traits such as temperature tolerance; produce sterile organisms; map and store genetic material; introduce new traits not normally found in the species; improve the health of cultured organisms; and improve the quality and diversity of seafood products available for consumers (25,31). These technologies have great potential to continue to improve the productivity and profitability of the aquaculture industry. Traditional technologies such as selective breeding can be made more effective by combining them with newer methodologies such as DNA marking or marker-assisted selection.

Benefits from biotechnologies used in aquaculture have been realized and will continue to increase. The risks to the environment, human health, and other social concerns, however must be carefully evaluated before these technologies are widely adopted. To date there exist only voluntary performance standards for assessing and managing ecological risks of genetically modified fish and shellfish (2). A better documented database of risk assessment results are needed to establish appropriate regulations governing research, use, and release of genetically modified organisms that pose risks to the environment and human consumers. Guidelines could be established with involvement from the relevant federal and state agencies as well as representatives of the aquaculture industry, commercial fishing industry, environmental groups, and other stakeholders. Many of the biotechnologies perceived to pose the greatest risks to the environment or human health are not yet widely used, therefore, opportunity exists to prevent problems before they occur.