Chapter 10

New Products and Industries from Biodiversity

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*This appears in Appendix A at the end of this volume.

Main Messages

Bioprospecting is the exploration of biodiversity for new biological resources of social and economic value. It is carried out by a wide variety of industries that include pharmaceuticals, botanical medicines, crop protection, cosmetics, horticulture, agricultural seeds, environmental monitoring, manufacturing, and construction. There are between 5 million and 30 million species on Earth, each one containing many thousands of genes. However, fewer than 2 million species have been described, and knowledge of the global distribution of species is limited. History reveals that less than 1% of species have provided the basic resources for the development of all civilizations thus far, so it is reasonable to expect that the application of new technologies to the exploration of the currently unidentified and overwhelming majority of species will yield many more benefits for humanity.

Biodiversity is the fundamental resource for bioprospecting, but it is rarely possible to predict which genes, species, or ecosystems will become valuable for bioprospecting in the future. A wide variety of species—microbial, plant, and animal and their genes—have provided services, products, blueprints, or inspiration for products or the basis of industries. While species-rich environments such as tropical forests may be expected to supply many products in the long term, bioprospecting thus far has yielded valuable products from many diverse ecosystems, including temperate forests and grasslands, arid and semiarid lands, freshwater ecosystems, and montane and polar regions, as well as cold and warm oceans. In this context, the conservation of all biodiversity in all ecosystems would provide the most opportunities for bioprospecting in the future.

Well-regulated bioprospecting contributes to the joint goals of ecosystem conservation and social and economic development through partnerships and benefit-sharing. Bioprospecting can achieve multiple goals: generating revenues for protected areas, conservation projects, and local communities; building scientific and technological capacity to study and manage biodiversity; enhancing biodiversity science; raising awareness of the commercial and noncommercial importance of biodiversity; creating businesses dependent upon the sustainable management of resources; and, in rare instances, generating large profits for corporations and shareholders. These benefits may occur at local, regional, or national scales.

Market trends vary widely according to the industry and country involved, but many bioprospecting activities and revenues are expected to increase over the next decades. Several major new industries, such as bioremediation and biomimetics are well established and appear set to increase, while others have a less certain future. The current economic climate suggests that pharmaceutical bioprospecting is likely to increase, especially as new methods that use evolutionary and ecological knowledge enhance productivity.

Bioprospecting is one part of a package of economic activities that, when carefully implemented, use biodiversity in a way that contributes to the multiple objectives of the sustainable management of natural resources, poverty reduction, and economic development. Established biodiversity-based industries such as farming, forestry, grazing, and fisheries, along with local uses of biodiversity for foods, medicines, and fibers and for cultural activities and the development of new industries such as bioremediation, ecological restoration, and biomimetics, generate knowledge of and respect for the multiple benefits of biodiversity. While recent research clearly demonstrates the future resource potential of biodiversity, opportunities for bioprospecting industries in any given country will depend on many factors, ranging from the conservation status of its biodiversity to the trends in a variety of markets.

Global threats to biodiversity, and especially species losses, may affect the development of valuable new products for humanity, including medicines, industrial processes, and new crop varieties. The current global decline of biodiversity may affect bioprospecting in many ways. Serious undervaluation of such losses for bioprospecting result from a lack of recognition that a high proportion of commercially important species are either small or microscopic, and so losses go undetected. Other threats include loss of traditional knowledge, the impacts of some kinds of modern agricultural technologies, and depletion of natural resources.

Bioprospecting partnerships are increasingly supported by international and national laws and self-regulation measures, including codes of ethics, high-quality contracts, and transparent institutional policies that result in benefit-sharing. Recent international agreements include the 1992 Convention on Biological Diversity and the 2001 International Treaty on Plant Genetic Resources for Food and Agriculture. More than 100 countries have introduced or are developing laws and other policy measures that complement these international initiatives, regulating access to biological resources and benefit-sharing. Further, a range of documents developed by indigenous communities, researchers, professional associations, and bioprospecting companies has generated a significant shift in the ethical and legal framework within which bioprospecting operates. Nevertheless, serious issues remain, including achieving an appropriate balance between benefit-sharing and the creation of incentives for investment. These often-conflicting interests among potential partners may operate across local, national, and international scales.

10.1 Introduction

The number of species of use to humanity runs into many thousands, and those that form the basis of contemporary agriculture are well known—not least the major crops and domesticated animals that provide food (Baker 1978; Clutton-Brock 1999). Indigenous peoples use a very wide range of lesser-known species and often possess deep ecological knowledge that helps maintain the ecosystems in which they live (Myers 1983; Malaisse 1997).

In this context, it is widely assumed that the biological resources of the world have been thoroughly explored. Recent research shows that our knowledge of biodiversity is still very limited, however, and that the exploration of all types of organisms is likely to yield many more useful species for an unexpectedly wide variety of human needs and pursuits. To place this in perspective, flowering plants (angiosperms) have provided a wide variety of foods, drugs, cosmetics, fibers, and building materials. But it is now clear that this group of organisms, in its entirety, constitutes only a minor part of the total number of species on Earth and that vast resources remain in other species-rich groups such as the microbes and invertebrates (Wilson 1992; Torsvik et al. 2002; Crawford and Crawford 1998; Eisner 2003).

Some environments are also little explored. This is especially true of the oceans, where current exploration is revealing many new species every week and scientists expect to discover at least 2 million marine species over the next two or three decades. This may be an underestimate, however, as the number of species of marine nematode worms alone has been estimated at 1 million (Malakoff 2003). Even apparently well known groups such as the mammals and reptiles are revealing new species (Beattie and Ehrlich 2004), and recently a new family of frogs has been discovered in southern India—a major surprise, as amphibians have been studied intensively for decades (Hedges 2003).

The importance of the exploration of biodiversity for new products was recognized at the 1990 meeting of the International Society of Chemical Ecology in Goteborg, Sweden, in the Goteborg Resolution (Eisner and Meinwald 1990): "Natural products constitute a treasury of immense value to humankind. The current alarming rate of species extinction is rapidly depleting this treasury, with potentially disastrous consequences. The International Society of Chemical Ecology urges that conservation measures be mounted worldwide to stem the tide of species extinction, and that vastly increased biorational studies be undertaken aimed at discovering new chemicals of use to medicine, agriculture and industry. These exploratory efforts should be pursued by a partnership of developing and developed nations, in such fashion that the financial benefits flow in fair measure to all participants."

This chapter explores modern and emerging biodiversity-based products and industries and largely excludes traditional ones that have been developed throughout history. However, traditional uses of biodiversity are included when they have contributed to new ventures. The next section presents the multiple and disparate facets of bioprospecting across a wide range of industries. The third section discusses the variety of partnerships and benefit-sharing arrangements that have developed worldwide. The fourth section reviews the legal environment for bioprospecting, and the final section summarizes the major threats to the industry.

10.2 Overview of Industries Involved in Bioprospecting

Bioprospecting involves the use of a wide variety of species by a wide variety of industries (ten Kate and Laird 1999; Beattie and Ehrlich 2004). Some examples are provided in Table 10.1. The resource values of the species concerned to date have differed fundamentally in nature—in some cases it is the organism itself that provides the product, while in others the organism serves as a model or as inspiration for a copy, modified or otherwise. The examples given here are a small part of a much longer list and have been selected because they are either the subject of major ongoing investment or already a commercial reality.

Discovery is often achieved by considering where the desired product might have evolved naturally. Habitats or a group of organisms are then identified and explored. An example of the discovery and development of a product with self-cleaning properties is presented in Box 10.1.

Another example is the search for heat-tolerant industrial enzymes. As most enzymes are destroyed by heat, some industrial processes would be greatly enhanced if heat-tolerant enzymes were discovered. The question of where heat-tolerant enzymes would be expected to occur was pursued by exploring the microbial biodiversity of thermal springs. These habitats revealed microbes with heat-stable enzymes that are being applied to a variety of industrial processes, including paper and pulp manufacturing, biotechnology, commercial cleaning, and forensic science, with each generating important benefits or major revenues (e.g., see Moss et al. 2004). A possible new source of industrial enzymes of this type is the recently discovered bacterium *Pyrodictium,* which inhabits hydrothermal vents and can grow at temperatures between 85 and 121 degrees Celsius (Kashefi and Lovley 2003).

Other methods of drug discovery include combinatorial chemistry and rational drug design. While these have been developed independently of natural products, current thought is that natural products are likely to provide the best lead-molecules in the future (Chapman 2004; Ortholand and Ganesan 2004).

10.2.1 Pharmaceutical Bioprospecting

Interest in novel products from biodiversity has varied greatly in the last decade, with a general decline in pharmaceutical bioprospecting by major companies, although a resurgence is expected (Chapman 2004). Based on the knowledge that many important drugs, such as aspirin, were derived from natural products (Jack 1997)—that is, generated in the tissues of native species—the industry has at various times invested heavily in the exploration of species-rich communities such as rain forests and coral reefs in search of commercially profitable pharmaceuticals (Ismail et al. 1995; Bailey 2001).

Alarming levels of antibiotic resistance in many human pathogens is likely to provoke an increase in pharmaceutical bioprospecting, which remains a vital source of lead drug discovery (Wessjohann 2000; McGeer and Low 2003; Newman et al. 2003). Malaria, one of the world's most deadly diseases, has been treated historically with drugs derived from natural products—quinine, chloroquine, mefloquine, and doxycycline—and today the artemisinins derived from the Chinese herb Qinghao (*Artemesia annua*) are at the forefront of the battle against this parasite.

Some compounds from natural resources approved for marketing during the 1990s in the United States and various other countries are shown in Table 10.2. The probability that any single discovery actually reaches the marketplace remains low, however. For example, 75% of the drugs that entered phase 1 clinical trials in the Untied States in 1991 went on to phase 2, 36% entered phase 3, and only 23% received FDA approval. From another perspective, the probability of a drug being launched into the market was 5–10% during the pre-clinical research and development phase, 30% during phase 2A, 40% during phase 2B, 70% in phase 3, and 90% during the period of regulatory review (ten Kate and Laird 1999). This is because the conventional process of drug discovery has several distinct and increasingly expensive stages: acquisition of the natural material; extraction of the active compounds; primary screening against a range of human disease organisms; isolation and chemical characterization of the active compounds; secondary screening assaying the compounds in tissue cultures and experimental animals; structural chemistry and synthesis; pre-clinical development with a view to human trials; and clinical development, marketing, and distribution.

The magnitude of the resource was illustrated by Henkel et al. (1999), who provided a summary of the wide range of organisms from which drugs have been derived, including bacteria and fungi (both terrestrial and marine), plants, algae, and a variety of invertebrates, including worms, insects and mollusks. (See Figure 10.1 in Appendix A.)

Munro et al. (1999) demonstrated the importance of marine animals among diverse organisms screened for clinically significant cytotoxicity (such as is useful for anti-cancer drugs) and compared the relative importance of terrestrial versus marine organisms for this particular pharmaceutical activity. (See Figure 10.2.) They also showed the widespread distribution of this cytotoxicity among marine phyla, reminding us that many are relatively little known either to the general public or to the bulk of scientists. They include the Porifera (sponges), Bryozoa (sea mosses), Cnidaria (jellyfish), and Echinodermata (starfish and their relatives). (See Figure 10.3.)

Natural products are still important sources of novel compounds for pharmaceuticals. An average of 62% of new, small-molecule, nonsynthetic chemical entities developed for cancer research over the period 1982–2002 were derived from natural products. In antihypersensitive drug research, 65% of drugs currently synthesized can be traced to natural structures. This emphasizes the important role of many natural products as blueprints rather than the actual end points. Newman et al. (2003), who assembled these data, noted that they had not been able to identify a *de novo* combinatorial compound approved as a drug during

Table 10.1. Novel Products and Industries and the Organisms They Come From. The examples shown have either been the subject of major investment and research or have become commercial products. (Classification from Margulis and Schwartz 1998)

Category	Common Name	Phylum	Ecosystem of Origin
Products			
Antibiotics	ants, mollusks, plants, bacteria	Mandibulata, Mollusca, Anthophyta, Actinobacteria	terrestrial (e.g., temperate and tropical forests), marine
Antifreeze, cryoprotectants	fish, water bears	Craniata, Tardigrada	polar, marine, montane
Cold-active enzymes	fungi	Ascomycota	Antarctica
Self-cleaning surfaces/paints	various plants	Anthophyta	terrestrial (including wetlands)
Architectural design	termites	Mandibulata	mounds from tropical arid ecosystems
Fire detection devices	fire beetles	Mandibulata	temperate forest
Pest repellants	various insects	Mandibulata	terrestrial (including temperate forests and grasslands)
High-tensile fibers	spiders, moths	Chelicerata, Mandibulata	terrestrial (most ecosystems)
Surgical drugs	scorpions, wasps	Chelicerata, Mandibulata	terrestrial
Clinical drugs	leeches, fungi	Annelida, Basiodiomycota	terrestrial, aquatic
Fiber-optics	sponges	Porifera	marine
Industrial enzymes (textiles, pulp and paper)	primitive bacteria, fungi	Crenarchaeota, Ascomycetes, Basidiomycetes	terrestrial, aquatic, marine, extreme environments
Engineering materials, (ceramics, industrial crystals)	snails	Mollusca	marine
Model research organisms in science/medicine	slime moulds, round worms	Myxomycota, Nematoda	terrestrial, marine
Industrial adhesives	barnacles, velvet worms, gecko	Crustacea, Onychophora, Craniata	ocean, forest
Antifouling paints	sea moss, marine algae,	Bryozoa, Rhodophyta	marine coastal
Robotic and aeronautic design	fish, millipedes, bees, dragonflies, worms	Craniata, Mandibulata, Annelida	all ecosystems
Industrial pigments	single-cell algae	Dinomastigota Bacillariophyta Haptomonada	marine
Industries			
Nanotechnology	bacteria, viruses, algae	various	various (e.g., terrestrial, marine)
Biological mining	bacteria	various	terrestrial, aquatic
Biological control, crop protection (new developments)	many different groups	various: microbes, animal, plant	various
Biomonitoring (new developments)	many different groups	various: microbes, animal, plant	various (e.g., terrestrial, aquatic, marine)
Agriculture, horticulture (new developments)	mostly plants	Anthophyta	various (terrestrial)
Biomimetics	many different groups	various: plants, animals, microbes	various (e.g., terrestrial, marine)
Ecotourism	all groups	various	wide variety of tourism destinations
Bioremediation	mostly microbes	various (e.g., Proteobacteria)	various
Ecological restoration	mostly plants but invertebrates/ microbes being tested	various	various
Pharmaceuticals	many different groups	microbes, plants, animals	various
Botanical medicines	mostly higher plants	Anthophyta	various
Personal care/cosmetics	many different groups	various	various

this time frame, despite massive investment in this technique by pharmaceutical companies. (See Figures 10.4 and 10.5.) Some of the most striking examples of recent drug development based on natural products are the drugs that inhibit cell division. (See Table 10.3.)

The current assessment of bioprospecting by the large pharmaceutical companies is reflected in the focus of their research and development, where the major investment is in rational drug design and combinatorial chemistry (Olsen et al. 2002; Hijfte et al. 1999) rather than natural products. Such decisions have probably been based on three factors: recent advances in high throughput instrumentation, low ''hit'' rates from natural product exploration, and consequently the high risks of natural product investment. On the other hand, natural product bioprospecting is

BOX 10.1

The "Lotus Effect," an Example of Novel Products Commercialized through the Exploration of Biodiversity

Many important processes in nature occur at the interfaces between organisms and their environment. For example, the outermost barrier of plant leaves and shoots, the cuticle, can be regarded as an extracellular membrane deposited on the outer epidermal cell wall and is the necessary interface for plant-environment interactions. It is covered with epicuticular waxes that self-assemble into complex three-dimensional crystals. They are very important in repelling water, and this hydrophobicity occurs in extreme forms when the crystals generate the micro- and nano-roughness of about 0.2–5 μm. This leads to what is known as super-hydrophobicity, so that the leaf surface is never wetted. Water forms spherical droplets, due to surface tension, that rest on the outermost tips of the wax crystals.

After screening some 15,000 species by electron microscopy, it has been shown that micro- and nano-rough plant surfaces are self-cleaning. Dirt particles cannot adhere to the surface, and the contact area between them and the surface is extremely reduced, while at the same time the contact between the water droplets and the dirt particles is increased, resulting in greater adhesion to the water droplet. This super-hydrophobicity results in self-cleaning plant surfaces in the presence of rain, fog, or dew. The cleanliness originates from the combined effect of surface topography and hydrophobicity.

Research has shown it is possible to transfer this effect into biomimetic self-cleaning products, and in 1994 a patent process was initiated. In 1998 a European patent was granted, yielding the trademark Lotus-Effect®. Research and development involving 12 industrial companies led to more than 200 patents. In 1999 a facade paint named Lotusan® was successfully launched on the market, and there are now more than 350,000 buildings with self-cleaning coatings. The enormous range of industrial applications for these biomimetic surfaces comprise mainly external materials exposed to rain, such as the surfaces of buildings and vehicles. However, some special applications such as medical devices, pipelines, and textiles are being targeted. In the near future, architectural glass, awnings, and temporary spraycoats with Lotus-Effect® are expected on the market. Detailed information is available at www.lotus-effect.com.

the main activity of a variety of active small companies that sell their products to the larger ones that can afford the massive costs of drug development. Some contemporary researchers believe that natural product research is more likely to result in new lead discovery and that the great advantage of combinatorial chemistry is its capacity to take advantage of such leads. Chapman (2004) and Ortholand and Ganesan (2204) argue persuasively for this approach.

10.2.2 Ethnobotanical Bioprospecting

Historically, much corporate drug discovery has depended on indigenous knowledge delivered to modern science through ethnobotany. Over 50% of modern prescription medicines were originally discovered in plants, and plants continue to be the source of significant therapeutic compounds to this day (e.g., Pearce and Puroshothaman 1993; Cragg and Newman 2004). Many were developed because the plants were used in indigenous medicine, and some common drugs were first used only on a local scale. In Europe, for example, aspirin was first isolated from *Filipendula ulmaria* because it had long been used in folk medicine to treat pain and fevers. When the Bayer company developed a synthetic derivative of salicylic acid called acetylsalicylic acid, they named it Aspirin—"a" for "acetyl" and "spirin" for *Spiraea,* the former Latin name for the genus. Another European folk cure that became a drug was derived from *Digitalis purpurea,* the leaves of which were first used to treat congestive heart failure. The active ingredients, digitoxin and diyoxin, remain an important treatment for heart ailments.

Farnsworth et al. (1985) showed that at least 89 plant-derived medicines used in the industrial world were originally discovered by studying indigenous medicine. Among the best known is quinine, used in South America to treat fever. This has been the single most effective cure for malaria. Quinine comes from the bark of trees of the genus *Cinchona* that grow in the Andean region. More recently, the drugs vincristine and vinblastine were discovered in the rosy periwinkle (*Catharanthus roseus*) from Madagascar. When the Eli Lilly company studied this plant, they found that the periwinkle had anti-cancer properties. Vincristine has given children with leukemia a likelihood of remission, and vinblastine has cured many people with Hodgkin's disease. Native American peoples used the mayapple (*Podophyllum peltatum*) to treat warts. Two important drugs have been derived from it: teniposide to treat bladder cancer and podophyllotoxin, from which a powerful anti-tumor agent has been synthesized. The biological origins of the top 150 prescription drugs in the United States are shown in Table 10.4.

Indigenous peoples generally have large pharmacopoeias, since plants are often the only source of medicine available to them. Ethnobotanical studies list a large number of plant species used medicinally (e.g., Cox and Balick 1994; Balick 1994; Peters et al. 1989; McCutcheon et al. 1992). The MA Sub-Global Mekong River Wetlands Assessment has identified 280 medically important plant species, 150 of which are in regular use. The ethnobotanical approach to drug discovery is more likely to succeed where people have lived in the same area over many generations and so have had more time to discover suitable medicines. Local medicines can be complex mixtures of chemicals, however, either from the whole plant or from several plant species, and their efficacy may be enhanced from interactions that take place in their preparation or consumption. Thus, when pharmacologists try to isolate individual chemicals from the plants they often do not achieve the same effect as the local preparation. This is one reason that many effective cures of indigenous peoples have not been developed by western medicine.

10.2.3 The Botanical Medicine Industry

Botanical medicines in commerce are generally whole plant materials as opposed to pharmaceuticals, which are often derived from specific biochemical compounds extracted from plants. Best-selling examples include ginkgo, St. John's wort, echinacea, garlic, ginseng, and various yeasts. (See Table 10.5.) The structure of this industry varies according to the particular medicines being produced, but typically there are several stages: collection from the wild or cultivation, followed by the purchase of materials by exporters, importers, wholesalers, brokers, or traders. Materials may then be tested for contamination, powdered, or extracted by processing companies or by manufacturers of the finished products. These may then be handled by specialized distributors before retailing to consumers.

Revenues from these products can be very large. For example, annual sales of medicinal ginkgo, garlic, evening primrose, and echinacea in Europe average $350 million (ten Kate and Laird 1999). The global sales of raw botanical materials by leading U.S.

Table 10.2. Some Compounds from Natural Sources Approved for Marketing in the 1990s in the United States and Elsewhere. These agents are either pure natural products, semi-synthetic modifications, or the pharmacophore is from a natural product. (From ten Kate and Laird 1999 with permission)

Generic	Brand name	Developer
In the United States and elsewhere		
Cladribine	Leustatin	Johnson & Johnson (Ortho Biotech)
Docetaxel	Taxotere	Rhône-Poulenc Rorer
Fludarabine	Fludara	Berlex
Idarubicin	Idamycin	Pharmacia & Upjohn
Irinotecan	Camptosar	Yakult Haisha
Paclitaxel	Taxol	Bristol-Myers Squibb
Pegaspargase	Oncospar	Rhône-Poulenc
Pentostatin	Nipent	Parke-Davis
Topotecan	Hycamtin	SmithKline Beecham
Vinorelbine	Navelbine	Lilly
Only outside the United States		
Bisantrene		Wyeth Ayerst
Cytarabine ocfosfate		Yamasa
Formestane		Ciba-Geigy
Interferon, gamma-la		Siu Valy
Miltefosine		Acta Medica
Porfimer sodium		Quadra Logic
Sorbuzoxane		Zeuyaku Kogyo
Zinostatin		Yamamouchi

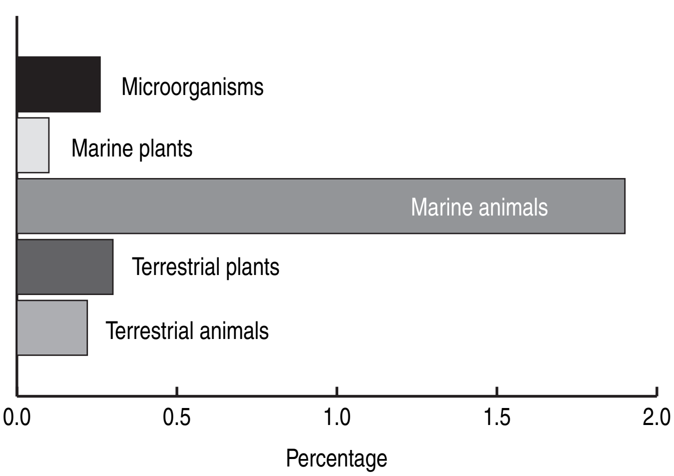

Figure 10.2. Distribution of Samples with Significant Cytotoxicity among Marine and Terrestrial Organisms (Munro et al. 1999)

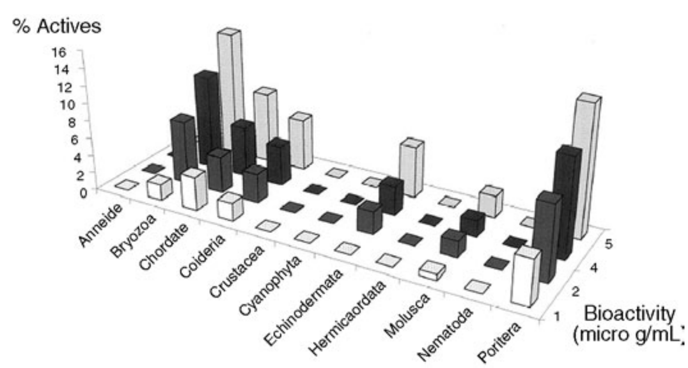

Figure 10.3. Distribution of Cytotoxicity among Marine Phyla (Munro et al. 1999)

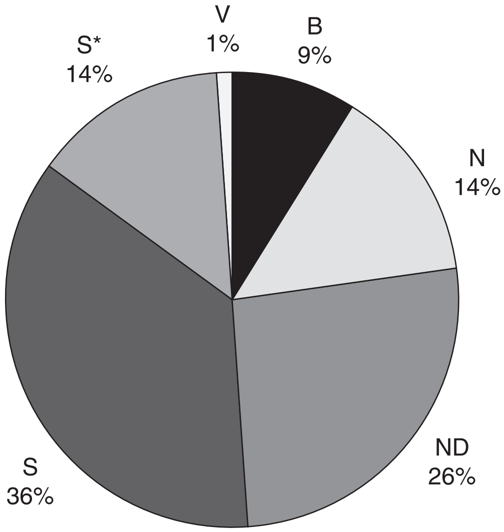

Figure 10.4. Sources of All New Chemical Entities, 1981–2002 (n = 1031). (Newman et al. 2003) B = biological, N = natural product, ND = derived from a natural product, S = totally synthetic drug, S* = totally synthetic but the pharmacophore was from a natural product, V = vaccine, NM = natural product mimic, i.e., designed from knowledge gained from a natural product.

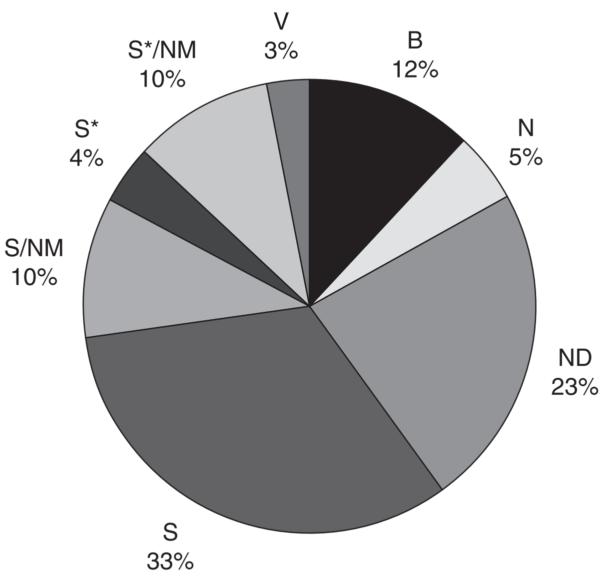

Figure 10.5. Sources of All Available Anti-cancer Drugs, 1940s–2002 (Newman et al. 2003) B = biological, N = natural product, ND = derived from a natural product, S = totally synthetic drug, S* = totally synthetic but the pharmacophore was from a natural product, V = vaccine, NM = natural product mimic, i.e., designed from knowledge gained from a natural product.

suppliers amount to approximately $1.4 billion (ten Kate and Laird 1999).

The ''nutraceuticals'' industry sells food ingredients or products believed to confer health or medical benefits. These include dietary supplements, individual nutrients, foods enhanced in various biotechnological ways, and fortified foods. Major products of this industry include dietary additives. Products include teas with added ginseng, probiotic yogurts, fruit juices fortified with calcium, and flour fortified with folic acid. Various companies in the food industry have been interested in sugar substitutes such as the sweet-tasting proteins produced by plants such as *Dioscoreophyllum cumminisii, Thaumatococcus daniellii,* and *Richardella dulcifera,* all from West Africa, and *Capparis masaikai* from South China.

The nutraceuticals market for 1996 was estimated at $16.7 billion (ten Kate and Laird 1999), and interest is rapidly growing worldwide. Further information resources on botanical medicines include the herbage database at www.herbage.info.

Table 10.3. Naturally Derived Microtubule Stabilizing Agents That Inhibit Cell Division and Are Useful against Cancer (Cragg and Newman 2003)

Name	Source	Status
Paclitaxel	*Taxus brevifolia* (plant) (made by semisynthesis)	clinical use
Docetaxel	semisynthesis from *Taxus* spp.	clinical use
Discodermolide	*Discodermia dissoluta* (marine) (made synthetically)	phase I in 2002
Eleutherobin	*Eleutherobia* sp (marine)	derivatives in preclinical development
Saracodictyin	*Sarcodictyon roseum* (marine)	derivatives in preclinical development
Epothilones	*Sorangium* sp. (terrestrial microbe)	naturally occurring compounds and derivatives in early clinical trials
Laulimalide	*Cacospongia mycofijiensis* (marine)	preclinical development
Dictyostatin-1	*Spongia* sp. and a deep-water Lithistid sponge (marine)	preclinical development
Jatrophane esters	*Euphorbia semiperfoliata* (plant)	preclinical development

Table 10.4. Biological Origins of Top 150 Prescription Drugs in the United States (World Resources Institute 2000, with permission, based on Grifo et al. 1997)

Origin	All Compounds	Natural Product	Semi-Synthetic	Synthetic	Share of Total
	(number)				*(percent)*
Animal	27	6	21	–	23
Plant	34	9	25	–	18
Fungus	17	4	13	–	11
Bacteria	6	5	1	–	4
Marine	2	2	0	–	1
Synthetic	64	–	–	64	43
Total	**150**	**26**	**60**	**64**	**100**

10.2.4 The Personal Care and Cosmetics Industries

Personal care and cosmetics industries use wild harvested or cultivated products in a wide variety of products, including cosmetics, feminine hygiene, hair products, baby care, nail care, oral hygiene, deodorants, skin care, and fragrances. Different demo-

Table 10.5. Geographic Range of 1,464 Medicinal and Aromatic Plants in Trade in Germany, 1997 (ten Kate and Laird 1999, with permission)

Geographic Range	Medicinal and Aromatic Plant Species Found Only in the Region	Introduced Species	Total Medicinal and Aromatic Plant Species Found in the Region
Europe	16	71	605
Africa	63	16	343
Asia – temperate	248	13	849
Asia – tropical	90	10	318
Australasia	8	18	55
Pacific	1	1	13
North America	124	186	454
South America	106	25	207

graphics apply to their marketing; different products are directed to "prestige," "mass," and "alternative" markets.

The same agents and organizations as those that handle botanical medicines often handle the raw materials for these industries, which consist largely of dried plant products and oils from a wide variety of organisms. Many of the natural products of interest are derivatives of wild sources and include saponins, flavonoids, amino acids, anti-oxidants, and vitamins as well as various compounds from seaweeds, chitin from crustaceans, and fish oils. In some specialty markets, products are certified as being from organic or sustainable sources and others as "fair trade" products—that is, ethically or socially certified.

The value of this industry was estimated at $1.4 billion for the United States for 1996 and at $2.8 billion for 1997. Growth is also thought to be very rapid in markets as varied as Asia, Latin America, Europe, and Australia.

10.2.5 Biological Control and Crop Protection

Biological control is a more established biodiversity-based industry but it is currently expanding through new knowledge of biodiversity (Bellows 1999). Much biological control is for crop protection, using predators, parasites, or pathogens or their products to limit pests. (See Box 10.2.)

Biological control has also been used on many invasive species, however, including non-crop pests—chiefly animals and plants introduced outside their native environments that have successfully bred, often in vast numbers, uncontrolled by their natural enemies. (See Chapter 4 for a further discussion of invasive species.) In this context, biological control has been successfully implemented against rabbits in Australia, Europe, Argentina, and Chile; against cats in oceanic islands; and against various plant species that have escaped from gardens. The application of biological control as crop protection includes the control of soil pathogens; the protection of tree crops such as olives, citrus, coffee, bananas, and coffee; use in tree plantations, greenhouses, and grape vines; and the control of weeds in both terrestrial and aquatic environments as well as medical and veterinary pests.

Biocontrol is an industry that involves bioprospecting activity worldwide, particularly in developing alternatives to chemical pesticides that have severe environmental and occupational safety hazards. Bioprospecting for this industry requires study of the diversity both of the organism being controlled as well as the control agent(s). Biological control agents include plants, viruses, bacteria, fungi, insects, nematodes, and many other kinds of invertebrates and have been extremely successful in many parts of the world (Bellows and Fisher 1999). (See Box 10.3.)

Because nearly all these control agents are small organisms, however—many of them microscopic and with no appeal to the public—they have not been recognized as being in need of conservation action, even when threatened with extinction. In recent years, pests have been controlled by the simultaneous release of more than one control agent; for example, the so-called Bridal Creeper, a noxious vine, is controlled by a fungus, a beetle, and a leafhopper insect in Australia. None of the three control species were considered to have any economic importance until their utility in the biocontrol industry was demonstrated.

The biocontrol industry has had major problems when control agents introduced to areas where their own natural predators were absent have themselves become pests or plagues. In response, new and more rigorous screening protocols for new biological control agents have been developed so as to minimize the risks of such population explosions. These new developments have significantly increased the environmental safety and commercial viability of the biological control industry (Bellows 1999).

Box 10.3 illustrates the potential benefits of maintaining all species, most notably as a resource for the crop protection and biological control industries. In the specific case cited, sufficient weevil species were still extant in the host country, facilitating the discovery of the control agent. Such a situation has been repeated all over the world both for this and for the biological monitoring industry (Bellows and Fisher 1999).

The best data on the commercial value of biological control come from the crop protection markets, from which it is estimated that sales by the top 10 crop protection companies in 1997 totaled $25 billion. It is unclear what fraction of this total can be assigned to the use of species and species products, as they are used in many different ways, but there are also several billion more dollars spent on research and development. An alternative valuation method to crop protection sales figures has been suggested by Pimentel (1992), who examined the varied and multiple costs of pesticide use for food production in the United States. These costs included health bills of human applicators, veterinary costs, surface and groundwater contamination, pollinator losses, and administrative costs. The estimated total was $8 billion a year, much of which could be avoided by the replacement of chemical pesticides with biological control agents.

10.2.6 Biomimetics

Biomimetics is the generic name for a wide variety of biologically inspired technologies. The industries involved use the structures and materials of organisms as the models, blueprints, or inspiration for novel materials and manufactured products (Mann et al. 1989). Among the best-known examples are the shell and radula (teeth) of various mollusks that have informed the manufacture of high-tech ceramics and other materials, including car parts and industrial crystals. Another high-profile research program is the application of the properties of spider silk to the manufacture of novel high-tensile fibers (Beattie and Ehrlich 2004; Mann 2001; Craig 2003).

The most recent development is in the field of molecular biomimetics, which is providing much of the inspiration and design for nanotechnology (Sarikaya et al. 2003). The field has its own professional journal, *Biomimetics,* and the Darwinian theory of evolution by natural selection was in a sense reworded by Birchall (1989) for this context: "Biology does not waste energy manipu-

BOX 10.2

The Role of Biological Materials in Crop Protection (modified from ten Kate & Laird 1999 with permission)

Chemical Control

Natural products:

"Pure" natural products (isolated from nature and not changed chemically

Semisynthesized derivatives (modifications of compounds isolated from nature)

Synthetic compounds:

Synthetic analogue compounds built from templates originally discovered from natural products

"Pure" synthetic compounds (not based on a natural product lead)

Behavior-modifying chemicals:

Use of naturally derived and synthetic versions of signaling chemicals from living organisms, such as pheromones, to create insect traps and disrupt mating

Growth regulators:

Insect growth regulators: chemicals that interfere with the growth of pests

Plant growth regulators: chemicals such as gibberillic acid sprayed on to crops to increase the size and quality of fruit, to speed/delay ripening

Biological Control

Toxic protein-producing bacteria:

Over 30 recognized subspecies of the naturally occurring bacterium *Bacillus thuringiensis (Bt)* produce different insecticidal toxins

Baculoviruses:

Naturally occurring ("wild type") or modified viruses that, once ingested by insects, interfere with their metabolic processes and kill them

Fungal pesticides:

Fungal insecticides: three species of fungi are the main source of fungal insecticides—*Verticillium, Metarhizium* and *Beauvaria*

Fungal herbicides: fungi that affect the metabolic processes of weed species, killing them

Fungal fungicides and microsporidia

Bacterial pesticides:

Bacterial bactericides, bacterial fungicides, and bacterial insecticides

Natural predators, parasites, and parasitoids:

A wide variety of species, including many arthropods and nematodes, that seek out and kill pests

Crop Improvement

Genes for disease and pest resistance or herbicide tolerance:

Breeding resistance or tolerance into crop varieties, using either traditional methods or genetic engineering

BOX 10.3

Water Weeds and Weevils: The Importance of Individual Species to the Biological Control Industry

Salvinia is an aquatic fern from South America that has been accidentally carried beyond its natural area of distribution to localities where it has no natural enemies that regulate its growth. As a result, in many parts of the world it completely covers the surface of lakes, rivers, and canals with a deep layer of vegetation that prevents sunlight penetrating the water below. There are many damaging flow-on effects, such as the decline of light-dependent animals and plants, reduction in the oxygen content of the water, and overwhelming bacterial growth.

The Australian Commonwealth Scientific and Industrial Research Organisation searched for a biological control agent in its native environments in South America and a promising herbivorous weevil was discovered, cultured in large numbers and then released. Nothing happened. A second species of weevil that appeared to be very similar was tried, and this succeeded in reducing the weed with spectacular speed and success. (The photos in Appendix A show a lake before and several months after the introduction of the weevil.)

There were two interesting lessons from this experience. First, if you have seen one weevil you definitely have not seen them all! Second, you never know which species are going to be crucial. In this case, a tiny, little-known weevil from South America was worth millions of dollars by restoring water quality and enabling the return of fisheries and commercial waterway navigation throughout a large part of Australia. Biological control agents that fight crop pests are often equally obscure and yet have great value—not merely in terms of dollars but also in terms of human lives.

lating materials and structures that have no function and it eliminates those that do not function adequately and economically. The structures that we observe work and their form and microstructure has been developed and refined over millions of years . . . it is well, then, to look for fresh insights to biology at the wisdom encapsulated in the materials it uses."

Beattie and Ehrlich (2004) discuss a wide variety of examples. At present, the use of biomimetics is scattered throughout a variety of engineering, manufacturing, and construction industries, and it is difficult to identify its commercial worth or to predict its value in the future. Clearly, however, individual projects and products generate very large revenues.

10.2.7 Biomonitoring

Biological monitoring is an industry developing in response to the necessities of tracking down sources of pollution across large geographical areas. This would normally require vast resources in terms of conventional instrumentation, but the status of the environment can also be monitored by using organisms that routinely "sample" the environment, such as aquatic or marine filter-feeding animals. Provided that the species used are both widespread and common and that collection for lab testing does not compromise their populations, there is little need for instrumentation outside the analytical laboratory (Boyle 1987; Rosenberg and Resh 1993). Biomonitoring is also applied to the detection of pollutants in soils and may involve a range of selected test organisms, including bacteria, algae, earthworms, and nematodes. A selection of biomonitoring organisms is provided in Table 10.6.

10.2.8 Horticulture and Agricultural Seeds

The global horticulture industry is worth many billions of dollars, mainly based on cultivated plants. Although all horticultural spe-

Table 10.6. Types of Biomonitoring and the Organisms Used

Type	Common Name	Phylum
Freshwater	fish	Craniata
	insect larvae	Mandibulata (e.g., Ephemeroptera, Plecoptera, Trichoptera)
	mussels	Mollusca
	water fleas	Crustacea
	bristle worms	Annelida (Oligochaeta)
	mosses	Bryophyta
Soil	earthworms	Annelida (Oligochaeta)
	round worms	Nematoda
Marine	paddle worms	Annelida (Polychaeta)
	fish	Craniata
	sea squirts	Urochordata (Tunicata)
	bacteria	Proteobacteria
Air	bees, ants	Mandibulata (Hymenoptera)
	lichens	Mycophytophyta
Monitoring disturbance and rehabilitation	ants, butterflies, beetles, spiders	Mandibulata Chelicerata

cies are derived from wild species, current reliance on wild plant biodiversity is limited to a few areas, notably flowers harvested from native plants and genetic material taken from native plants to improve or establish new horticultural varieties. This is not to minimize the size or cost of the industrial effort developing new varieties, and the revenues they generate are large. For example, it is estimated that it can cost up to $5 million to develop a single new variety (ten Kate and Laird 1999).

The industry is made up of companies of all sizes—from large multinationals to small, local enterprises—and is backed up by specialized research organizations in many countries. These include universities and botanic gardens as well as commercial laboratories. The contemporary wild harvest may be small, as the commercial focus is generally on developing new varieties of familiar and popular plants, such as roses, hydrangeas, geraniums, and begonias. However, in some areas seed harvesting remains large-scale (and sometimes a problem, as described at the end of the chapter).

The development of new seed varieties for agriculture is a major use of plant biodiversity, some of it from wild, native plants, but much of it from the wealth of crop varieties that have been bred to adapt crops to a host of local conditions worldwide (Brush 2004). Contemporary technologies usually take advantage of very long development times. For example, the production of one wheat variety may involve thousands of plant breeding crosses and dozens of different individual lines, including wild ones, from many countries and over many centuries (see, e.g., Mujeeb-Kazi et al. 1996; Quick et al. 1996; Cassaday and Smale 2001). New varieties are developed through traditional plant breeding protocols, genetic engineering, or a combination of these two. The research budgets for agricultural biotechnology are estimated at $1.95 billion annually but only a small proportion of this involves the harvest of seeds from the wild.

Although most agricultural and horticultural varieties are derived from seeds collected from wild plants at some time in the past, the sources of almost all plant breeding materials today are seed banks maintained by major corporations, universities, botanic gardens, and regional, national, or international gene banks. There are many reasons for this, especially the time and expense required to take seeds from wild plants and breed them for compatibility with commercial varieties. There is serious concern about the growing genetic uniformity of crops, however, and about the availability of genes from wild ancestors and neglected varieties used to generate adaptive variety. With the burgeoning biotechnology industry developing ever more sophisticated genetically engineered crops, it is difficult to know what the demand will be for wild seeds in the future. Some of the key issues are summarized in Box 10.4.

10.2.9 Bioremediation

A more recent example of the potential for novel biodiversity-based industries is bioremediation. This industry is often associated with heavy industry and mining, especially in countries where the law requires restoration of abandoned industrial sites and mines (Crawford and Crawford 1998). Two common methods are applied by this industry: first, remediation by altering the site environment to allow resident, beneficial microorganisms to proliferate or, second, augmentation of the site by the addition of beneficial microbes. Both these methods explore microbial diversity not just for species tolerant to the pollutants concerned but those that metabolize them, either transforming them into less harmful derivatives or sequestering them from other species in the ecosystem. Success has often been hard to achieve, but in some

BOX 10.4

Some Reasons the Use of Wild Plant Resources May or May Not Increase (from ten Kate & Laird 1999 with permission)

Why demand for primitive germplasm may grow in the future:

- The need to improve resistance to disease requires access to more genes and the globalization of research and markets means that pests and disease are transferred faster, increasing demand for access.
- Breeders wish to broaden the genetic base of the material they use.
- The desire to move away from reliance on chemical pesticides to more biological approaches will require access to diverse genetic resources.
- Modern methods make it easier to use primitive materials.
- Public funds are drying up, so companies will need to access more diverse materials themselves.

Why demand for primitive germplasm may decrease in the future:

- It is becoming harder to gain access to materials from many countries.
- Fear of accidental infringement of patents and a reluctance to negotiate licenses and material transfer agreements will decrease the demand for access to cultivars.
- Modern methods mean there is more to be found in existing collections and less need to turn to primitive materials.
- Privatization and commercialization of research mean that the public institutions that were accessing materials are no longer doing so. It is less competitive for companies to work on unimproved materials.

cases highly toxic sites have been transformed into relatively benign areas suitable for other purposes (Flatman et al. 1994; Rittman and McCarty 2001). Microbial inoculation for the remediation of major oil spills is showing increasing promise (Mueller et al. 1992).

One example of fungal bioremediation illustrates that exploring biodiversity is key to the success of this technology and that the function of a microorganism in nature can be applied to a quite different twenty-first century commercial need. The major bioremediating fungi are white rot fungi, so-called because they degrade the dark-colored lignin in wood, leaving behind light-colored cellulose and giving WRF-decayed wood a bleached appearance. These fungi are common and diverse in forests worldwide and are a vast ''bank'' of chemical systems that have evolved to break down intractable materials such as wood. Without the chemical activity of WRF and other fungi known as brown rot fungi, the natural recycling of nutrients would be extremely slow.

The lignin-degrading systems of white rot fungi are now of major commercial importance because they also degrade many classes of pollutants such as PCBs, dibenzo dioxins, and dibenzo furans that have chemical properties in common with lignin (Joshi and Gold 1993). The industrial uses and potential of microbial biodiversity are further reviewed in Demain (2000), and the new technologies known as bioaugmentation, in which selected microorganisms are added to polluted substrates such as soils, are described fully by Mueller et al. (1992).

10.2.10 Ecological Restoration

Ecological restoration differs from bioremediation in that it attempts to recreate the ecosystem that once existed. In terrestrial situations, while some of the original structure is often achieved with rudimentary soils, some leaf litter, and elements of the vegetation, the restored species richness is generally reduced in comparison with the former ecosystem. Nevertheless, restoration is a much needed industry worldwide as a result of national and local government legislation requiring the repair of damaged ecosystems such as abandoned industrial and mining sites, eroded agricultural lands, and surface water degraded by a wide variety of human activities.

This demand has generated a new industry with active societies such as the Society for Ecological Restoration. The basic resource is biodiversity (Handel et al. 1994) and the species used are most often those from neighboring or comparable ecosystems that can be carefully harvested or grown offsite and moved to the restoration site (Harker et al. 2001; Whisenant 2001). Effective ecological restoration requires deep knowledge of species, their ecological functions, and their interactions with each other and the environment.

Agroforestry is discussed here not because it is used only for ecological restoration but because it has become such an important activity in this field. Simons and Leakey (2004) report as follows: ''In recent years international aid to developing countries has developed a strong focus on poverty reduction. In parallel with this, the World Agroforestry Centre (formerly ICRAF) initiated its tree domestication program in the mid-1990s with a new focus on products with market potential from mainly indigenous species. With this came a shift from on-station formal tree improvement towards more active involvement of subsistence farmers in the selection of priority species for domestication and the implementation of the tree improvement process. In many regions in which ICRAF is active, farmers selected indigenous fruit trees as their top five priorities. Consequently, over the last decade a strategy for the domestication of indigenous trees producing high-value products of traditional and cultural significance has been developed.''

This approach to improving the trees planted by farmers has many advantages (Leakey 1999):

- It has a clear poverty reduction focus, which has been endorsed by a review on behalf of the U.K. Department for International Development. The income derived from tree products is often of great importance to women and children.
- It has immediate impact by being implemented at the village level, thereby avoiding delays arising from constraints to the transfer of technology from the field station to the field that can be due to technical, financial, dissemination, and political difficulties.
- The approach being developed is focused on simple, low-cost, appropriate technology yielding rapid improvements in planting stock quality, based on selection and multiplication of superior trees that also produce fruits within a few years and at heights that are easily harvested.
- It builds on traditional and cultural uses of tree products of domestic and local commercial importance and meets local demand for traditional products.
- It promotes food and nutritional security in ways that local people understand, including promoting the immune system, which is especially important in populations suffering from AIDS.
- It can promote local-level processing and entrepreneurship, hence employment and off-farm economic development. These benefits can stimulate a self-help approach to development and empower poor people.
- It can be adapted to different labor demands, market opportunities, and land tenure systems and is appropriate to a wide range of environments.
- It builds on the rights conferred by indigenous knowledge and the use of indigenous species by the Convention on Biological Diversity and is a model for best practice.
- It builds on the commonly adopted farmer-to-farmer exchange of indigenous fruit tree germplasm as practiced in West and Central Africa—for example *Dacryodes edulis,* although native to southeast Nigeria and southwest Cameroon, is now found across much of the humid tropics of central Africa.
- It builds on the practice of subsistence farmers to plant, select, and improve indigenous fruits, such as marula (*Sclerocarya birrea*) in South Africa, where the yields of cultivated trees increased up to 12-fold and average fruit size is 29g, while trees in natural woodland are 21g (Shackleton et al. 2003).
- The domestication of new local cash crops provides the incentive for farmers to diversify their income and the sustainability of their farming systems.

Against these advantages there are possible disadvantages, such as reduced genetic diversity in wild populations as domesticated populations replace them. However, the implementation of some in situ or ex situ conservation of wild germplasm, together with the deliberate selection of relatively large numbers of unrelated cultivars, can minimize these risks. Indeed, the current situation, whereby each village develops its own set of cultivars, should maintain levels of regional intraspecific diversity.

To maximize the economic, social, and environmental benefits from domestication, it is crucial to develop post-harvest techniques for the extension of shelf life of the raw products, processing technologies to add value to them, and, of course, access to markets. Without this parallel preparation for increased commercialization, domestication will not provide all the benefits just described. The combination, however, has potential applications that extend beyond subsistence agriculture to agricultural diversification of farming systems. In tropical North Queensland, Australia, for example, this is linked, at least in part, to the development of an Australian "bush tucker" food industry supplying restaurants and supermarkets.

10.2.11 Ecotourism

Ecotourism is an industry in which tour operators prospect for localities rich in biodiversity or charismatic species. As returns on investment rely greatly on maintaining such attributes, it is in the interests of the industry to conserve many elements of biodiversity. Tourists are less likely, for example, to travel to rain forests or coral reefs that are degraded or to mountains and islands that have been deforested. In the majority of destinations, biodiversity is one of the main attractions for ecotourists. The Quebec Declaration on Ecotourism states that "ecotourism embraces the principles of sustainable tourism and contributes actively to the conservation of natural and cultural heritage and includes local and indigenous communities in its planning, development and operation, contributing to their well-being" (www.uneptie.org/pc/tourism/ecotourism/home.htm).

Ecotourism can generate large revenues, some of which goes to local communities, but it is often extremely difficult to make it sustainable, as the industry itself can also put major pressures on biodiversity: Local increases in the human population from both tourists and the employees that look after them, along with hotel, road, airport, and dock construction and off-road travel, can all contribute to local pollution, habitat fragmentation, lowering of water quality, and the influx of exotic plants and animals. In some cases, these activities lead to declines in the very animals the industry is built around (WRI 2000). Ecotourism often relies heavily on the presence of what are known as charismatic animals and plants, and it can be especially vulnerable to losses in biodiversity, which are occurring on a global scale and therefore threatening the sustainability of this industry. (See Chapter 17.)

10.2.12 Other Biodiversity-based Industries and Products

Other products and industries are also emerging, many of which depend on microbial diversity. These include a wide variety of microbially produced enzymes that contribute to treating industrial and agricultural wastes, driving diverse reactions in chemical engineering, processing wood and pulp, increasing the efficiency of textile manufacture, and industrial and domestic cleaning. Biological mining uses microbes that leach metals from low-grade ores and mine tailings. Biofuels, especially ethanol, are derived from a wide variety of plant species, and various microbial species generate biogas from landfills and waste dumps (ten Kate and Laird 1999; Beattie and Ehrlich 2004). Each of these applications is already a commercial reality, and almost any one of them may surpass the other biodiversity-based industries in commercial value in the future, assuming the development of appropriate markets.

10.3 Distribution and Value of the Resource

Biodiversity is global, and the long history of its use by humanity, together with the more recent history of bioprospecting, shows that important commercial species have been found in all parts of the world. Indeed, it appears impossible to predict in which ecosystems and therefore in which countries future products will be found.

At this point it is reasonable to ask if bioprospecting will be more profitable in species-rich areas of the world, particularly the sub-tropical and tropical forest areas and coral reefs. The evidence does not present a clear picture. Many biological resources have been derived from non-tropical areas, including some critical medicines such as aspirin and the drugs derived from the plant genera *Digitalis, Podophyllum,* and the Pacific Yew tree *Taxus brevifolia,* all of which are from temperate zones. Other products such as cryoprotectants and anti-freezes have come from cold-water fish and high-altitude arthropods. Materials for silk research and development, industrial adhesives, and mollusk-based ultrastructures have been derived from native species in a wide variety of non-tropical ecosystems, both terrestrial and marine. In addition, microbes for bioremediation and biological mining and species used in the biological control of agricultural pests and in biological monitoring have emerged from ecosystems at a wide variety of latitudes and altitudes.

With respect to ocean resources, a variety of drugs are derived from different non-tropical marine organisms such as tunicates, which have provided anti-tumor compounds currently undergoing clinical trials, and marine fungi that secrete powerful antibiotics (Rinehart 2000; Cueto et al. 2001). Tunicates and marine fungi inhabit the intertidal zones of oceans in many parts of the world, including temperate regions. Some industrial bioprospecting also takes place in extreme environments such as hot springs and the poles or at great oceanic depths, where the variety of species may be relatively low, but the species present are unique to those areas and harbor extremely valuable adaptations to high or low temperatures or to great pressures (see, e.g., Moss et al. 2003).

Much recent pharmaceutical bioprospecting has focused on species-rich ecosystems, especially tropical rain forests and coral reefs. Although there is a general trend of increasing species richness with lower latitudes and altitudes, these trends do not necessarily inform bioprospecting. Certainly, if the goal is to screen as many species as possible in the most cost-effective way, the use of species-rich ecosystems such as rain forests appears logical. In addition, evolutionary theory tells us that herbivory, especially by insects, is far more intense in the tropics than in the temperate zones. In this context, plant chemical defenses against herbivory are likely to be both stronger and more diverse in ecosystems such as tropical rain forests, and this may make some pharmaceutical bioprospecting more profitable in tropical than in temperate forests (Coley et al. 2003).

However, many areas of modern bioprospecting are even more target-orientated, asking, for example, where the desired product is most likely to have evolved. In this context, there is frequently no expectation that it has necessarily evolved in a species-rich ecosystem, but rather that it has evolved in response to a particular kind of natural selection. Thus cryoprotectants will have evolved in animals from extremely cold environments, and silk is a predatory device that has evolved in all kinds of terrestrial environments. It may be that certain kinds of biological resources emerge as being more frequent in species-rich ecosystems, but far more research is required to discover which ones. The current expectation is still that novel drugs are more likely to come from the tropics.

Various methods of valuing biodiversity were reviewed by Heywood et al. (1995), and further discussion of the valuation of ecosystem services can be found in Chapter 2. The wide variety of products, especially drugs that have been derived from ecosystems, may suggest that there are likely to be many more awaiting discovery, and therefore biodiversity is a vast source of future revenues. While the evidence presented in this chapter suggests that this is likely to be the case, more specific quantitative economic analysis may be required to further understand the likely returns on investment from bioprospecting. An appraisal of these is presented in Box 10.5.

The current reality is that there is no robust, reliable, and generally agreed way of assessing the commercial value of the novel biological resources of any given species, group of organisms (taxon), habitat, or ecosystem. The situation is exacerbated by the fact that we are still in the early stages of discovery, and many resources are assumed to be there but are as yet unknown. Species useful to society or industry can be obscure, microscopic, and from any habitat and the use may be derived from a gene, a product, a behavior, or a structure, thus values can be legitimately anticipated but their dimensions tend to emerge later.

There have been many attempts at establishing the commercial value of drugs derived from wild or cultivated species with a view to valuing the biodiversity from which they came. (See Table 10.7.) Farnsworth et al. (1985) estimated that 25% of prescriptions from community pharmacies in the United States during the period 1959–80 contained a compound derived from higher plants. The contribution of wild species has not diminished, as 57% all prescriptions in the United States for the period January–September 1993 contained an active compound derived from biodiversity (Grifo and Rosenthal 1997).

Even more recently, Laird and ten Kate (2002) reported on the findings by Newman and Laird (1999): "They found that natural products continue to be a major player in the sales of pharmaceutical agents: 10 of the 25 best-selling drugs in 1997, representing 42% of industry-wide sales, are either biological, natural products, or entities derived from natural products, with a total 1997 value of US$17.5 billion. The study also found that a significant portion—between 10% and 50%—of the ten top-selling drugs of each of the top 14 pharmaceutical companies are either natural products or entities derived from natural products."

Early estimates of the annual value of individual medicinal plant species ranged between $203 million and $600 million (Farnsworth and Soejarto 1985; Principe 1989). More recently, however, the drugs Taxol and Taxotere derived from a single species *T. baccata* yielded $2.3 billion in drug sales during 2000. While this suggests that individual species may be of very great value, it does not necessarily show that biodiversity conservation is a prerequisite for bioprospecting. For example, sales of the drug Navelbine derived from the rosy periwinkle (*C. reseus*) were worth $115.4 million in 2000, but this is a common tropical garden plant. Yet bioprospecting activities are valuable in several other ways, not least providing education and training, employment, and local and regional sources of revenues based on the harvesting, processing, manufacturing, distribution, and retailing of products.

Mendelsohn and Balick (1997) estimated the value of as-yet-undiscovered pharmaceuticals from plants in tropical forests at $109 billion. They noted that a severe constraint on this value was the high cost of finding the pharmaceuticals but that this cost could be reduced by ethnobotanical methods. Costs could be further reduced by ecologically driven discovery methods (Coley et al. 2003), especially if they were applied to a broader range of organisms including, for example, microbes and arthropods.

BOX 10.5

Some of the Principles and Problems of Valuing Biodiversity and Biological Resources

Several principles are important in considering the economic value of bioprospecting. First, economic values are determined on the margin. This means that values must be placed in the context of particular magnitudes of change. If the great majority of Earth's biodiversity were to be lost, the value of the lost opportunities for inventing and improving products would be astronomical. Less value would be foregone if fewer components of biodiversity were at risk.

Second, research and development is an inherently random process, and the outcomes are uncertain. The value to be assigned to a change in the biodiversity available for conducting research is related to the increase in the expectation of the outcome it affords.

Third, value is determined by scarcity. If there is a lot of something, a little more or less of it does not make much difference. Conversely, unique resources command large values because there are no substitutes for them.

These are illustrated by a thought experiment (modeled after Simpson et al. 1996). Suppose there are many species that might provide the source of a particular new product. Many analyses of the value of bioprospecting have focused on the expected reward to success: the probability of making a "hit" times the payoff from developing a successful product. However, the value of biodiversity on the margin—what we might label the value of the "marginal species"—is the incremental increase in the expected reward to success. It is the probability of making a "hit" times the payoff times the probability that none of the other species available for testing would have yielded the same success.

While commentators often emphasize the rewards accruing to success, other considerations may be more salient. As the number of species researched increases, the value of having more necessarily declines and, in the limit, vanishes. This can be explained as follows. If the probability that any one species chosen at random will yield a success is relatively high, it is unlikely that it will be necessary to test a large number of species in order to achieve a success. Conversely, if the probability of success in testing any one species is low, it is unlikely that two or more will prove redundant, but also unlikely that any will prove successful. Regardless of the likelihood of success in any given test, the value of the "marginal species" will be small when the number of species is large.

The same species may, of course, be tested for any of a number of different applications. Thus, in order to calculate the overall value of the "marginal species," one would have to sum the values in all potential applications, both current and anticipated. If there are relatively large numbers of species available for testing, comparably large numbers of potential applications would need to be identified for the value of the "marginal species" to be appreciable (although if new products complement one another, values may be greater; Craft and Simpson 2001). Moreover, not all species are equally attractive as potential research leads. Other things being equal, organisms that are "most different" from others will be more valuable. This is not because they are necessarily more likely to yield new products, but rather because they are more likely to yield new products in the event that other, more distantly related, organisms do not (Weitzman 1992).

Knowledge is also valuable. Researchers will test first those organisms most likely to yield a success and will be willing to pay more to do so (Rausser and Small 2000). The fact that some organisms are known to promise more leads means, necessarily, that others are considered less promising and less valuable. If promising prior information is available on the properties of species from better-known regions, the bioprospecting value assigned to the as-yet undescribed species of the world's remaining pristine ecosystems will be commensurately lower.

Table 10.7. Some Values for Plant-based Pharmaceuticals
(Pearce and Moran 1994, adapted from Principe 1989)

Value	United States	OECD	World
		(billion 1990 dollars)	
Market value of trade in medicinal plants	5.7	17.2	24.2?
Market or fixed value of plant-based drugs on prescription	11.7 (1985) 15.5 (1990)	35.1 (1985)	49.8? (1985)
Market value of prescription and over-the-counter plant-based drugs	19.8 (1985)	59.4 (1985)	84.3 (1985)
Value of plant-based drugs based on avoided deaths:			
Anti-cancer only	120.0	360.0	
+ non-cancers	240.0 (1985)	720.0 (1985)	

Notes: Bracketed year indicates year estimate refers to.
Ratio of OECD to United States taken to be 3.
Value of statistical life taken to be $4 million in 1990 prices.
Lives saved taken to be 22,500–37,500 per annum in United States. Average is taken here (i.e., 30,000). Multiply OECD by 1.4 to get world estimates.

10.4 Recent Industry Trends

Most novel products are researched, developed, and produced in industrial countries, and there is a geographical mismatch between centers of biodiversity, which tend to be in the tropics, and centers of research and development, which are largely concentrated in the temperate zones (Barbier and Aylward 1996; Simpson and Sedjo 1996). With respect to pharmaceutical bioprospecting, while tropical/temperate partnerships have been formed and some developing countries are beginning to enter the industry independently, the prevailing situation is that the resources are currently considered most likely to be located in the tropical regions while the value creation in terms of development and manufacturing as well as consumption frequently takes place elsewhere.

The withdrawal of many of the largest pharmaceutical companies from bioprospecting during the last decade is based in part on the experience that large investments have yielded relatively few lead compounds for development. In recent years, several laboratories and some small companies, located in different parts of the world, have applied natural history knowledge and ecological and evolutionary criteria and theory to increase lead discovery.

For example, Coley et al. (2003) carried out pharmaceutical bioprospecting in the tropical forests of Panama. The theory of plant defense against attacks by herbivores predicts that older leaves and many other plant tissues are protected, at least in part, because cell walls are toughened by cellulose and lignin, neither of which is of medical importance. By contrast, young leaves must expand and so cannot be protected by such stiff, physical means but rather by repellent chemicals. The crucial inference is that young, expanding leaves will contain a greater variety of more active secondary metabolites than older leaves or other plant parts. By focusing specifically on the collection of young leaves, the team has isolated a variety of novel molecules that they have tested for activity against three cancer cell lines, Chagas' disease, leishmaniasis, malaria, and HIV, and the research has identified some promising bioactive leads.

This approach, which exploits the vast databases of natural history together with ecological and evolutionary theory, has been given a variety of names, including ecologically driven drug discovery, the biorational approach, and hypothesis-driven drug discovery (Beattie and Ehrlich 2004; Coley et al. 2003). It is too early to assess the impact of these methods, except to say that such sampling of ecosystems for potential drugs is a major advance on the more traditional pharmaceutical protocols. This, in turn, is likely to increase the frequency of lead discovery and thus the value of the industry as well as its resource. In recent years, these methods of bioprospecting have been applied to many industries outside pharmaceuticals (see Table 10.8), including biological control, bioremediation, construction engineering, shipping, environmental monitoring, mining, industrial materials, manufacturing, and environmental restoration. These developments suggest a far greater role for bioprospecting in the future because they lead to more species being identified as useful for a much greater variety of human activities.

10.5 Benefit-sharing and Partnerships

Benefit sharing and the creation of partnerships within diverse bioprospecting industries can be both complex and time-consuming. Since many legal issues were largely clarified in the Convention on Biological Diversity, the protection of the rights of indigenous communities and source countries has often created tensions, with the investment sector concerned with altered levels of returns and profitability (Dalton 2004).

The chain of events leading to sales frequently involves multiple stages that include generating the appropriate knowledge, harvesting, processing, manufacturing, and distribution. Accordingly, the economics of each stage vary greatly, and assigning and protecting intellectual property is often an underlying factor. When agreements are reached, however, the types of benefits are varied and may include benefits to society such as increased food production, better health, and cleaner environments; benefits to the local suppliers such as employment, training, and capacity-building, and benefits to local, regional, national, or international corporations in the form of profits. Most current partnerships also emphasize the benefits of biodiversity conservation.

10.5.1 Examples of National and International Agreements and Partnerships on Ethnobotanical Bioprospecting

The CBD calls for fair and equitable sharing of benefits arising out of the utilization of genetic resources, including appropriate access to genetic resources. The application of the CBD has supported the intellectual rights of indigenous peoples. For example, scientists at Trivandrum Botanic Garden in India developed two medicines from plants used by tribal people, and royalties from the sale of these drugs now benefit the hill tribes that provided the original leads. A drug suitable for treating obesity is being developed by the CSIR in South Africa in association with a pharmaceutical company and the local San peoples. The intellectual property involved San knowledge of the plant, *Hoodia,* which when consumed in appropriate amounts retards hunger and hence helps through periods of drought. The development of the drug

Table 10.8. Status and Trends in Major Bioprospecting Industries

Industry	Current Involvement in Bioprospecting	Expected Trend in Bioprospecting	Social Benefits	Commerical Benefits	Biodiversity Resources
Pharmaceutical	tends to be cyclical	cyclical, posible increase	human health, employment	+++	P,A,M
Botanical medicines	high	increase	human health, employment	+++	mostly P
Cosmetics and natural personal care	high	increase	human health and well-being	+++	P,A,M
Bioremediation	variable	increase	environmental health	++	mostly M
Crop protection and biological control	high	increase	food supply, environmental health	+++	P,A.M
Biomimetics	variable	variable, possible increase	various (e.g., medicine)	++	P,A,M
Biomonitoring	variable	increase	environmental health	+	P,A,M
Horticulture and seed industry	low	steady	human well-being, food supply	+++	P
Ecological restoration	medium	increase	environmental health	++	P, A, M

Key: +++ = billion dollars; ++ = million dollars; + = profitable but amounts vary
P = plants; A = animals; M = microorganisms

and the fate of the indigenous intellectual property have been complex. (See Box 10.6.)

The World Health Organization estimates that some 3.5 billion people in the developing world depend mainly on plants for their primary health care. The development of botanical medicines for local peoples is therefore an important contemporary area of research. In Brazil the "Plants of the Northeast" program has stimulated a "Green Pharmacies" initiative in which local cures are tested for efficiency and toxicity and then manufactured by local people at affordable prices. Many countries, such as Thailand, India, Sri Lanka, Mexico, and China, have integrated traditional medicine into their national health care systems. Ethnobotanical bioprospecting has therefore contributed both to the enhancement of local medicine and to the search for modern drugs.

The economic importance of biodiversity was formally recognized in the CBD, which emphasized the conservation of biodiversity, sustainable use of its components, and fair and equitable sharing of the benefits arising out of the use of genetic resources. This has also been recognized by a wide variety of other agreements in many parts of the world. For example, the 1993 meeting of the Asian Coordinating Group for Chemistry expressed concern over the number of Asian plant samples being removed for study elsewhere. Some cases involved biopiracy, as the host country had not given permission for the plants to be exported. The issue of ownership was also debated at the Seventh Asian Symposium on Medicinal Plants, Spices and Other Natural Products in 1992 in Manila, and a code of ethics was published as the Manila Declaration, which said, in brief:

BOX 10.6

Pharmaceutical Bioprospecting and Commercialization: Two Case Histories

Hoodia gordonia. Scientists at South Africa's Council for Scientific and Industrial Research isolated the chemical entity extracted from *Hoodia gordonia* called P57 that suppresses appetite. This plant property has been used by the San people for generations, staving off hunger during prolonged hunting trips. P57 was patented in 1996. Phytopharm plc, a listed British company, was licensed in 1997 by the CSIR to undertake development and commercialization, but in August 1998 the company signed a licensing agreement with Pfizer Inc for this purpose. In mid-2003 Pfizer informed Phytopharm that it would be discontinuing the clinical development and returned the rights to Phytopharm, which is presently negotiating with another company to do the clinical development.

With international support, the South African San Council demanded recognition of their knowledge and a share of the benefits, and an agreement with the San was signed in March 2003. The CSIR will pay the San 8% of the milestone payments made by its licensee, Phytopharm, during clinical development over the next few years and will offer study scholarships to the San community. The San could earn 6% of all royalties if and when the drug is marketed, possibly in 2008, and $32,000 has already been paid. San milestone payments could reach $1.8 million, while the royalties could be $9.4 million annually during the years before the patent expires. South Africa, Namibia, Botswana, and Angola are all involved, so income will go to the San Hoodia Benefit Trust that was established by the CSIR and the San.

Artemesia annua. This plant has been used by the Chinese to treat fevers for over 1,000 years. Extracts contain artemisinin that is effective against the malarial parasite, which is especially important where the parasite has evolved resistance to other drugs. It has several disadvantages, however, especially the difficulties of extraction and a short action time. In response, major programs have been established to generate superior derivatives, using the natural product as the blueprint.

One of the major players is the nonprofit Medicines for Malaria Venture established in 1999, which now funds and manages several projects, largely in partnership with the private sector, such as the Indian manufacturer Ranbaxy. This partnership has funded a research team at the University of Nebraska that has isolated a new class of synthetic endoperoxide antimalarials with superior properties to the original blueprint. In the future, other organizations, such as the National Institutes of Health in the United States, the Wellcome Trust in the United Kingdom, and the European & Developing Countries Clinical Trials Partnerships, aim to achieve far greater levels of participation by scientists and companies from developing countries.

- the biological resources of each region must be conserved,
- local scientists must be involved in research on local flora and fauna, and
- any commercial benefit arising from a regional resource must be shared equitably with the region.

This initiated a series of follow-up actions, including the 1994 meeting of ASOMPS in Malaysia, which produced the Melaka Accord that recognized the contribution of scientists from developing countries and sought legislation governing research into regional biological resources and sustainable development. The following year, Philippine Presidential Executive Order No. 247 was issued to regulate bioprospecting under two types of agreements: the Academic Research Agreement and the Commercial Research Agreement. And in 1996, Australia, Indonesia, Malaysia, the Philippines, and Thailand met in a UNESCO-funded a workshop in Kuala Lumpur that resulted in the Kuala Lumpur Guidelines on access to biological resources and sustainable development. This was followed by the Phuket Declaration issued by the International Conference on Biodiversity and Bioresources, which in line with the CBD stressed the protection of biodiversity, the sustainable utilization of biological resources, and the equitable sharing of commercial benefits. The 1998 meeting of ASOMPS in Hanoi urged the adoption of Philippine Executive Order No. 247 by other Southeast Asian nations. The state of Sarawak in Malaysia has passed The Sarawak Biodiversity Centre Ordinance to establish a Sarawak Biodiversity Centre and to regulate access to state biological resources.

While much pharmaceutical bioprospecting is still controlled by companies in industrial countries, there is a significant pharmaceutical industrial base emerging in developing ones as well. (See Table 10.9.) For example, Axxon Biopharm Inc. was established by a drug development program funded in part through grants from the International Cooperative Biodiversity Groups Program. The company seeks to commercialize nearly 100 leads in association with the Bioresources Development and Conservation Programme based in Nigeria. Flora Medicinal was established by Professor Jose Ribeiro da Silva in Rio de Janeiro and was recently acquired by Natura, a leading cosmetics and personal hygiene company.

Phyto Nova was established to research, develop, and market safe and affordable medicines for African wasting diseases, opportunistic infections, and other public health needs; to promote African traditional medicine, to scientifically validate natural products in order to ensure safety, efficacy and quality; and to ensure the sustainability of the supply of raw materials through conservation and local rural development. Centroflora, a Brazilian company, focuses on the production of organic, certified extracts from fruits and medicinal plants. The company, in association with the Brazilian Institute of the Environment and Renewable Natural Resources, selects local communities to engage in the organic production of medicinal plants to ensure good management and quality control. Each of the companies just mentioned use ethnomedical knowledge as the basis of drug development. In line with traditional concepts, the line between food and medicine is indistinct, so that products known as phytonutrients, nutraceuticals, phytofoods, and phytocosmetics are also generated.

Another kind of partnership has been formed by the government of Sarawak and the U.S. company Medichem Research: Sarawak-Medichem Pharmaceuticals is a joint venture in which both parties share the risks and the rewards. The Instituto Nacional de Biodiversidad (InBio) in Costa Rica has developed a complex of partnerships with pharmaceutical companies from many parts of the world, including Merck & Co., Indena, Eli Lilly and Co., and Agrobiot S.A., and a wide variety of academic institutions and other organizations such as the Rockefeller Foundation and the MacArthur Foundation. All agreements include aspects of access, equity, technology transfer, and training of local scientists as well as the nondestructive use of biodiversity (Sittenfeld and Gamez 1993).

Furthermore, returns go to the Ministry of the Environment and Energy to help cover conservation costs, and 50% of royalties go to national conservation areas. Through 2000, InBio donated \$400,000 to the Ministry for Environment and Energy for conservation, \$790,000 to conservation areas, \$713,000 to public universities, and \$750,000 to its internal programs, notably those inventorying Costa Rican biodiversity (Laird and ten Kate 2002). Similarly, there have been major initiatives with respect to bioprospecting, benefit-sharing, and capacity building in Nigeria, Guinea, and Uganda (Carlson et al. 1997; Carlson et al. 2001).

The International Cooperative Biodiversity Groups explicitly use their drug discovery and bioinventory research process to generate enhanced research capacity, opportunities for sustainable economic activity, and incentives for conservation at each host-country site. The approach emphasizes equitable sharing of the benefits of both the research process and its discoveries. This experimental program is administered by the Fogarty International Center of the U.S. National Institutes of Health and supported by NIH, the National Science Foundation, and the U.S. Department of Agriculture.

In its first 10 years of ICBG (1993–2003), eight projects involved researchers from over 59 organizations in 12 countries on five continents. (See Table 10.10.) Investments by the U.S. Government agencies in these projects totaled approximately \$29 million. Four major pharmaceutical companies, two agrochemical

Table 10.9. Examples of Pharmaceutical Developments in Biodiversity-rich Countries

Company	Country	Year	Number of Products	Number of Plant Species	Sales in 2002	Ethno-medical Leads	Benefit-sharing Policy
					(mill. dollars)		
Axxon Biopharm Inc.	United States/Nigeria	1999		10	not available	✓	✓
Centroflora	Brazil			21	21.5	✓	✓
Flora Medicinal	Brazil	1912	45	69		✓	
Phytonova Limited	South Africa	1999	4	3	0.2	✓	✓
Natura/Ekos	Brazil	2000	21	13	46.7	✓	✓
NuSkin	United States					✓	✓

Table 10.10. Projects of the International Cooperative Biodiversity Groups. Between 1993 and 2003, the ICBGs have comprised 17 projects working in 21 developing host countries, as well as the United States and the United Kingdom. In several cases partner institutions, particularly the pharmaceutical companies, have changed during the course of the project. As a result, those listed in any one group may include organizations that did not participate in the project at the same time. In addition to discovery of lead compounds for development of pharmaceuticals and agricultural agents, projects conduct research and training activities related to biological inventory, biodiversity conservation, benefit-sharing, and community development.

Years Active	Project Title, Country, Prospecting Focal Organisms	Principal Institutions Involved
1993–2008	Biodiversity Utilization in Madagascar and Suriname Suriname (1993–2003) and Madagascar (1998–2008) tropical plants (1993–2008), marine organisms (2003–08)	Virginia Polytechnic Institute and State University Missouri Botanical Garden; Conservation International; Madagascar National Centers for Pharmaceutical, Environmental and Oceanographic Research; Pharmaceutical Distribution Organization of Suriname (BGVS); Bristol-Meyers Squibb; Eisai Research Institute; Dow Agrosciences
1994–2000	Peruvian Medicinal Plant Sources of New Pharmaceuticals Peru tropical plants	Washington University (St. Louis) University of San Marcos (Peru); Peruvian Cayetano Heredia University; Searle-Monsanto Co.; Confederation of Amazonian Nationalities of Peru
1993–98	Chemical Prospecting in a Costa Rican Conservation Area Costa Rica arthropods	Cornell University Institute of Biodiversity (Costa Rica); University of Costa Rica; Bristol-Myers Squibb
1994–2003	Drug Development and Conservation of Biodiversity in West and Central Africa Nigeria and Cameroon tropical rainforest plants	Walter Reed Army Institute of Research Bioresources Development and Conservation Programme; Smithsonian Institution; University of Dschang (Cameroon); Pace University; University of Utah; International Center for Ethnomedical Drug Development (Nigeria)
1993–2003	Bioactive Agents from Dryland Biodiversity of Latin America Argentina, Chile, and Mexico arid lands plants, microorganisms	University of Arizona Argentine National Institute on Agricultural Technology; National University of Patagonia; Pontifical Catholic University of Chile; National Autonomous University of Mexico; Wyeth Pharmaceuticals; University of Illinois at Chicago; American Cyanamid Corp.
1998–2002	Drug Discovery and Biodiversity Among the Maya of Mexico Chiapas, Mexico temperate plants	University of Georgia College of the Southern Frontier; Molecular Nature Ltd. (UK)
1998–2008	Ecologically Guided Bioprospecting in Panama Panama rainforest plants (1998–2008), marine algae and invertebrates (2003–08)	Smithsonian Tropical Research Institute University of Panama; Oregon State University; National Secretariat for Science, Technology and Innovation (Panama); Gorgas Memorial Institute of Health Research; Monsanto; Novartis; Dow Agrosciences; Conservation International
1998–2008	Biodiversity of Viet Nam and Laos Viet Nam and Laos rainforest plants	University of Illinois at Chicago Purdue University; Research Institute for Medicinal Plants (Laos); Viet Nam National Institutes of Biotechnology, of Ecology and Biological Resources, and of Chemistry; Glaxo Smith-Kline; Bristol-Myers Squibb
2003–08	Conservation and Sustainable Use of Biodiversity of Papua New Guinea Papua New Guinea tropical plants, marine invertebrates	University of Utah Smithsonian Institution; University of Papua New Guinea; National Museum of Natural History (PNG); Wyeth Pharmaceuticals
2003–08	Building New Pharmaceutical Capabilities in Central Asia Uzbekistan, Kyrgyzstan temperate plants, terrestrial microbes	Rutgers University University of Illinois; Kyrgyz Agricultural Research Institute; Tashkent State Agrarian University; Diversa Corp.; Princeton University; Eisai Research Institute; Phytomedics, Inc.
Planning Grants 2003		
2003–05	Drug Development and Bio-cultural Diversity Conservation in the Pacific Islands Samoa, Tonga tropical plants, marine invertebrates, microorganisms	National Tropical Botanical Gardens, Hawaii AIDS Research Alliance; Samoan Ministry of Trade and Tourism; University of California; Anti-Cancer, Inc.; Diversa Corp.; Beth Israel Medical Center; Tongan Ministry of Agriculture and Forestry; Phenomenome Discoveries, Inc
2003–05	Potential Drugs from Poorly Understood Costa Rican Biota Costa Rica endophytic fungi, terrestrial microbes	Harvard Medical School National Institute of Biodiversity (Costa Rica)
2003–05	Drug Discovery and Biodiversity Conservation in Madagascar Madagascar plants, arthropods	State University of New York at Stony Brook University of Antananarivo, Madagascar; California Academy of Sciences; INDENA, Inc.; University of Eastern Piedmont, Italy
2003–05	New Drugs from Marine Natural Resources of Jamaican Reefs Jamaica coral reef organisms	University of Mississippi Discovery Bay Marine Laboratory; University of West Indies
2003–05	Studies of the Flora and Predator Bacteria of Jordan Jordan arid lands plants, bacteria	Research Triangle Institute Jordan University of Science and Technology; Virginia Polytechnic Institute and State University
2003–05	Biodiversity and Drug Discovery in the Philippines Philippines tropical plants, microorganisms, marine invertebrates	Michigan State University University of the Philippines
2003–05	Ecological Leads: Drugs from Reefs and Microbes in Fiji Fiji marine and freshwater organisms	Georgia Tech Research Corporation, School of Biology Scripps Institution of Oceanography; University of the South Pacific; South Pacific Applied Geoscience Commission; Bristol-Myers Squibb; Nereus Pharmaceuticals

companies, and two small biotech companies have at one time or another been affiliated with one or more projects. Private-sector support provided directly to the projects from partnering pharmaceutical companies, philanthropic foundations, and host-country governments totaled at least $2.5 million.

ICBG projects have variously focused on research and development with tropical, arid, or temperate plants, tropical arthropods, or endophytic and soil-associated microorganisms. Over 275,000 samples from more than 11,000 species of plants, 600 species of arthropods (mostly insects), and 500 species of microorganisms have been studied. Each group carries out assays on their own collections in multiple therapeutic areas, but almost all have an interest in cancer and malaria. Most groups also target a variety of infectious diseases, including parasitic and respiratory diseases that pose a high burden in the partner developing countries. Four have done work in agricultural areas, including veterinary medicines and insect, weed, nematode, and fungal pest control, predominantly through the industrial partners.

It is estimated that over 270 types of primary assays in 26 therapeutic and agricultural areas have been run over the 10-year life span of the project. Over 500 natural product compounds have been isolated that are active in one or more of the 22 therapeutic areas under study. Of these, approximately half are compounds new to science, but fewer than 50 have advanced to animal testing. Approximately 20 of these are currently considered active leads for drug development, although none has reached clinical trials to date.

Experiences from the first 10 years of the ICBG Program suggest that the industrial engines of innovation in drug discovery today are often small "biotech" companies rather than the pharmaceutical giants. This is especially true in natural products. Many large companies are no longer screening natural product samples because they take much longer to characterize and develop than synthetic molecules from their own libraries. The development of a natural product today usually involves a mix of large and small enterprises, none of which are well placed to undertake the entire task individually.

The pace of discovery of both taxonomically novel organisms and pharmacologically useful constituents has been shown to be higher today from marine and microbial sources than from the historically important plant kingdom, including tropical forests. And the low rate at which research on a newly collected organism leads to a commercial drug means that for the vast majority of projects the greatest benefits to development and conservation are likely to be gained from research, training, and technology transfer outcomes rather than from royalties on a marketed product.

10.5.2 Equity Considerations

Although bioprospecting research and development tends to be concentrated in industrial countries, the benefits to human well-being are often global. The principles for the treatment of intellectual property are well established (Rosenthal et al. 1999) and include protection of inventions using patents or other legal mechanisms; clear designation of the rights and responsibilities of all partners; sharing of benefits with the appropriate source-country parties; disclosure and consent of indigenous or other local stewards; information flow that balances proprietary, collaborative, and public needs; and respect for and compliance with relevant national and international laws, conventions, and other standards.

There is potential conflict between the routine scientific documentation of traditional medicines and the protection of indigenous intellectual property. For example, knowledge on the use of more than 1,100 medicinal plant species known to Malaysian peoples, including the Iban, Bidayuh, Orang Ulu, Malay, Kadazan, and Orang Asli, is now in the public domain, so it is no longer possible to seek compensation for sharing knowledge. However, some organizations are considering whether indigenous knowledge in the public domain might be protected in some way—for example, through the deployment of indigenous knowledge databases or by citing local people as "discoverers" and co-owners of patents.

The CBD provides guidance on these issues. Article 8(j), for example, calls for a fair and equitable sharing of benefits with indigenous peoples when their ethnobotanical knowledge is used in drug research and development. Access to biological resources in some resource-rich countries is now regulated, including in the ASEAN countries of Malaysia, the Philippines, and Thailand and in the Andean Pact countries of Bolivia, Colombia, Ecuador, Peru, and Venezuela. Permit processing regulations include a formal application, contract negotiation, and publication of the contract. Negotiations such as these are not easy, and there has to be considerable good will on all sides for the views of the host countries and the research institutions and industrial organizations to be accommodated. Benefit-sharing agreements have also been created in industrial countries such as Australia, for example, between the Australian Institute of Marine Science and the State of Queensland (see www.aims.gov.au/pages/about/corporate/bsa-aims-qldgov.html).

At the global scale, the CBD provides guidelines with respect to:

- terms for prior informed consent and mutually agreed terms;
- the roles, responsibilities, and participation of stakeholders;
- relevant aspects relating to in situ and ex situ conservation and sustainable use;
- mechanisms for benefit-sharing, such as through technology transfer and joint research and development; and
- the means to ensure the respect, preservation, and maintenance of knowledge, innovations, and practices of indigenous and local communities embodying traditional lifestyles relevant to the conservation and sustainable use of biological diversity, taking into account work by the World Intellectual Property Organization.

An Ad Hoc Open-ended Working Group on Access and Benefit Sharing was established by the CBD Conference of the Parties in 2000. The mandate of the Working Group is to elaborate and negotiate an international regime on access and benefit sharing within the framework of the CBD.

10.6 The Legal Environment

Many significant changes in the legal and policy framework over the past decade have set the scene for better recognition of the rights of indigenous and local communities in transactions involving genetic resources and traditional knowledge. These changes include intergovernmental agreements, national measures, and the various codes, statements, and policies adopted by communities, researchers, and companies.

10.6.1 Intergovernmental Agreements

In recent years, states have agreed on a range of intergovernmental agreements that include provisions supporting the rights of sovereign nations to control access to their genetic resources and the rights of local and indigenous communities to control the use of their traditional knowledge systems and thus benefit from them. Some agreements, such as the CBD, the Convention to Combat Desertification, and the International Labour Organization's Convention No. 169 Concerning Indigenous Peoples (in 1989), are legally binding. Others, such as the 1994 United Nations Draft Declaration on the Rights of Indigenous Peoples, *Agenda 21* from the Earth Summit, and the Rio Declaration of 1992, are not legally binding but place a moral obligation on signature countries to conform with the provisions.

The CBD's voluntary Bonn Guidelines on Access to Genetic Resources and Benefit-sharing provide operational guidance for ''users and providers'' of genetic resources and information for governments that are drafting national laws as well as for governments, communities, companies, researchers, and other parties involved in such agreements. The scope of the guidelines includes ''all genetic resources and associated traditional knowledge, innovations and practices covered by the CBD and benefits arising from the commercial and other utilization of such resources,'' with the exclusion of human genetic resources.

The guidelines describe steps in the access and benefit-sharing process, with sections on prior informed consent and mutually agreed terms as well as possible measures that countries and organizations should consider in response to their roles and responsibilities as providers and users of genetic resources and traditional knowledge. They outline recommendations for the participation of stakeholders and refer to incentive measures, accountability, national monitoring and reporting, verification, dispute settlement, and remedies. One appendix sets out suggested elements for material transfer agreements and another describes monetary and nonmonetary benefits that may be shared. The guidelines state that access and benefit-sharing systems should be based on an overall access and benefit-sharing strategy at the national or regional level. Given the complexity and uncertainty involved in access and benefit-sharing arrangements, such strategies can help communities and other groups to derive optimum benefits (ten Kate and Wells 2001).

Another recent development is the International Treaty on Plant Genetic Resources for Food and Agriculture, which has provisions on prior informed consent, benefit sharing, and farmers' rights. One important element of this treaty, which entered into force on 29 June 2004, is a multilateral system for access, for food and agriculture, to 35 crop genera and 29 forage species and associated benefit sharing. Its conditions for facilitated access to in situ plant genetic resources for food and agriculture allow for the protection of intellectual and other property rights. Benefits such as the exchange of information, access to and transfer of technology, and capacity building will be shared on a multilateral basis rather than with the specific provider of genetic resources.

Parties to this treaty agree that benefits should flow mainly to farmers involved in the conservation and sustainable use of plant genetic resources for food and agriculture, particularly in developing countries. The treaty encourages countries to take steps ''to protect and promote Farmers' Rights,'' including protection of traditional knowledge and the right to participate in benefit sharing and in national decision-making. Communities may also benefit through involvement in conservation and sustainable use.

10.6.2 Intellectual Property Rights

At regional and national levels, there are various initiatives to apply and develop intellectual property law consistent with prior informed consent for access to genetic resources, prior approval for the use of traditional knowledge, and benefit sharing. Of interest in this area are the U.K. Commission on Intellectual Property Rights and Decision 486, ''Common Intellectual Property Regime,'' of the Commission of the Andean Community, adopted in September 2000. The five Andean countries have attempted to introduce provisions in harmony with both the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights and the CBD. The decision provides that certain life forms shall not be considered inventions, that patent applications based on the region's genetic resources require a copy of an access contract, and that applications for a patent on an invention obtained or developed from traditional knowledge shall include a copy of a license from the community.

At the international level, there are discussions on the review and implementation of TRIPS (see, e.g., the Doha WTO Ministerial Declaration of November 20, 2001, paragraphs 17–19, and the TRIPS Council). The Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore of the World Intellectual Property Organization is considering intellectual property issues that arise in the context of access to genetic resources and benefit sharing, the protection of traditional knowledge, innovations and creativity, and the protection of expressions of folklore. For example, it is reviewing clauses related to IPRs in access and benefit-sharing agreements. WIPO is working on an electronic database of contract clauses and practices concerning access to genetic resources and benefit sharing. It is also considering elements of a sui generis system for the protection of traditional knowledge, and the Intergovernmental Committee has been considering ways to improve access to traditional knowledge for patent examiners so that patents are not improperly granted.

The African Model Law for the Protection of the Rights of Local Communities, Farmers and Breeders and for the Regulation of Access to Biological Resources aims to protect biodiversity and livelihood systems with a common tool (Ekpere 2001) and to guide African countries as they tailor national legislation and regional agreements dealing with the exchange of biodiversity knowledge, innovations, and practices.

A range of proposals has emerged concerning patents, from the meaning of ''prior art,'' the scope of patents, and the test of ''inventive step'' to procedural requirements such as disclosure of country of origin and even proof of prior informed consent in patent applications. Indigenous groups have engaged with the patent system to challenge the granting of patents. For example, the Coordinating Body of Indigenous Organizations of the Amazon Basin, an umbrella organization that represents more than 400 indigenous groups in the region, joined with the U.S.-based Center for International Environmental Law to file a request before the U.S. Patent and Trademark Office asking it to re-examine a patent issued on a purported variety of *Banisteriopsis caapi,* or Ayahuasca—a plant that has a long traditional use in religious and healing ceremonies. The patent was annulled shortly thereafter but has subsequently been reinstated. Other forms of IPRs are also being investigated as a potential source of protection against expropriation of traditional knowledge. Geographical indications and trademarks have looked particularly promising (see Commission on Intellectual Property Rights 2002).

10.6.3 National Laws on Access to Genetic Resources and Traditional Knowledge

The CBD establishes the sovereign rights of states over their biodiversity but leaves parties a great deal of discretion on regulation and access. About 100 countries have introduced or are developing appropriate national legislation and other policy measures. The Philippines and Peru have also introduced legislation to regulate access to traditional knowledge, whether it is obtained in conjunction with genetic resources or not.

The CBD states that the right to determine access to genetic resources rests with government, but several national laws on this topic make such governmental consent contingent on prior informed consent and benefit-sharing agreements with the communities involved. The Philippines and the five countries of the Andean Community were in the vanguard of such legislation. The Philippines Executive Order 247 on Access to Genetic Resources requires the prior informed consent of indigenous communities for prospecting for biological and genetic resources within their ancestral lands and domains. And the Indigenous Peoples Rights Act of 1997 in the Philippines recognizes a wide range of rights held by the country's numerous indigenous groups, including land rights and a considerable measure of self-government within ancestral domains, including rights to "preserve and protect their culture, traditions and institutions."

The Andean Community's Decision 391 established a Common Regime on Access to Genetic Resources in Bolivia, Colombia, Ecuador, Peru, and Venezuela. It states that an applicant wishing access to genetic resources, their derivatives, or their "intangible component" (any knowledge, innovation, or individual or collective practice of actual or potential value associated with them) within the region must secure prior informed consent from, and share benefits with, the respective government, any supplier of an "intangible component," and, where appropriate, from the "owner, holder or administrator of the biological resource containing the genetic resource." To complement this, in 2002 Peru introduced a law protecting the collective knowledge of indigenous peoples related to biological resources.

The Indian Biological Diversity Act 2002 stipulates that no foreigner may obtain any biological resource occurring in India or knowledge associated thereto "for research or for commercial utilization or for bio-survey and bio-utilization" without prior approval of the National Biodiversity Authority, nor may foreigners apply for any intellectual property right for any invention based on a biological resource obtained from India without the Authority's approval. A National Biodiversity Fund will channel benefits received from foreign bioprospectors to "benefit-claimers," to conservation, and to development for the area from which the genetic resource or knowledge comes. Indian citizens and corporations must also give "prior intimation" to State Biodiversity Boards before obtaining any biological resource for commercial utilization or biosurvey, through which benefits will be shared at the state level. Local bodies are to constitute Biodiversity Management Committees to promote the conservation, sustainable use, and documentation of biodiversity within the area.

National legislation is also being drafted to cover issues of access and benefit sharing relating to the use of genetic resources that originate outside the country in question. The Norwegian government, for example, is proposing such legislation to cover the use in Norway of genetic material originating elsewhere.

10.6.4 Indigenous Peoples' Declarations, Codes, Research Agreements, and Policies

Complementing developments on national and international policy, a range of codes of ethics, research agreements, statements and declarations, and corporate and institutional policies have been developed by indigenous peoples, researchers, professional associations, and companies, marking a significant shift in the ethical context for bioprospecting partnerships. Although implementation often remains a challenge, these have helped to make equitable relationships between local communities or indigenous peoples and various outside groups more likely and have influenced the language incorporated into national and international law and contractual agreements.

Over the past 20 years, indigenous peoples organizations have issued a range of declarations and statements with clear demands in terms of bioprospecting. These demands include ownership and inalienable rights over their knowledge and resources; requirements for their prior informed consent; the right of veto over research and access to their land, knowledge, or resources; and benefit sharing. Such demands have led to calls for a moratorium on bioprospecting pending a legal framework for equitable partnerships.

Researchers have developed a number of codes of ethics and research guidelines through professional societies such as the International Society of Ethnobiology, the American Society of Pharmacognosy, and the Society for Economic Botany. These lay out general principles for research partnerships, obligations of the partners, and sometimes recommended guidelines for researcher behavior in the field. Various research organizations have developed institutional policies that establish general principles for their employees and associates.

An important example is the Principles on Access to Genetic Resources and Benefit-sharing for Participating Institutions, in which 28 botanic gardens and herbaria from 21 countries developed common standards on access to genetic resources and benefit sharing. The Limbe Botanic Garden in Cameroon and other institutions working with indigenous peoples and local communities have endorsed these principles, then developed in more detail their own policies to translate them into action. These policies address practical issues confronted by the institutions concerned, including their relationship with local communities (Laird and Mahop 2001; and see www.rbgkew.org/peopleplants/manual).

An interesting further example is the Micro-Organisms Sustainable Use and Access Regulation International Code of Conduct to facilitate access to microbial resources and to help partners with agreements when transferring them. Partners in the voluntary code include several countries and both nonprofit and commercial organizations.

A number of bioscience companies have also developed corporate policies setting out their approach to compliance with the CBD. These policies generally describe the scope of resources covered by the policy; the standard to which the company means to be held accountable (for example, absolute commitments or commitments to make reasonable or best efforts); how to obtain prior informed consent and ensure genetic resources and information are obtained legally; and commitments to obtain clear legal title to the materials and information acquired, to share benefits fairly and equitably, and to support conservation through environmentally sustainable sourcing. Some corporate policies describe the process followed to develop them and the indicators used to gauge success in their implementation (ten Kate and Laird 1999).

In the GlaxoSmithKline Policy Position on the CBD approved in February 2002, the company states that it is increasingly focused on drug discovery by screening synthetic chemical compounds, and thus has limited interest in collecting and screening natural material. Collecting programs have drawn to an end, and screening is no longer conducted in-house but by partners in countries such as Brazil and Singapore. However, the policy supports the principles enshrined in the CBD when conducting relevant activities. The document does not address prior informed consent from local communities per se, but it states that the company has always undertaken only to work with organizations and suppliers with the expertise and legal authority to collect samples and to ensure that governments in developing countries are informed of and consent to the nature and extent of any collecting program.

10.7 Threats to and Impacts of Bioprospecting

A number of threats to biodiversity were discussed in Chapter 4, and each of these is also a threat to the sustainability of bioprospecting. The loss of biodiversity directly removes the resource base for bioprospecting, and declines in abundance of elements of biodiversity can reduce the ability and increase the costs of sampling. In addition to these main threats, the loss of traditional knowledge and modern agricultural practices have also contributed to declines in the potential for bioprospecting industries.

Bioprospecting itself also has had impacts on biodiversity, and many legal agreements now specify the need for sustainability with respect to issues such as harvesting from the wild. Sometimes, however, these issues are less relevant because the species of interest for bioprospecting are removed from the wild in such small numbers. For example, an individual termite under investigation for pharmaceutical analysis most likely involves a sample of a few hundred individuals from a single colony containing millions of individuals. Similarly, a bacterium taken from a gram of soil is cultured in the laboratory. At the other end of the spectrum, however, large quantities of species or products such as bark may be required for some pharmaceutical research and development, and special conservation measures may be required.

10.7.1 Biodiversity Loss

The current and future ability of countries, regions, and localities to generate novel products and industries is likely to be threatened by the loss of the basic resource, biodiversity, at all levels: genes, populations, species, and ecosystems. There is abundant evidence that such losses are widespread (see Chapter 4 and Balmford et al. 2003), and there is little sign that the losses are slowing, except in circumstances specifically aimed at biodiversity protection, such as the establishment of effective protected areas. (See Chapter 5 of MA *Policy Responses* volume.)

It is ironic that the recent explosion of new techniques in the biological, chemical, and physical sciences that has generated a vastly improved capacity to understand and use biodiversity has been accompanied by a global decline in this very resource. The loss of biodiversity may not only lead to a loss of commercial opportunity but may also compromise ecosystem function (see Chapter 11; Loreau et al. 2002; Coleman and Hendrix 2000). While there is much debate over exactly how many species are becoming extinct each year, it is abundantly clear that a very high proportion of species are losing their constituent populations at an alarming rate (Hughes et al. 1997; Ehrlich and Daily 1993).

In some forested regions there is a direct conflict of interest between logging on the one hand and human health and bioprospecting on the other. In Eastern Amazonia, for example, where native plants provide most of the medicines used locally, the removal of trees that supply medicinal leaves, fruits, bark, or oils has critically diminished the supply of medicines required by both the rural and the urban poor (Shanley and Luz 2003). Short-term, low-value commodities gained by logging may be matched by the sustainable use of non-timber forest products (Emery and McLain 2001) and, in rare instances, superseded by the high-value products that could be gained by bioprospecting.

For example, the pharmaceutically important tree species *T. brevifolia* was considered worthless to the timber companies logging the forests where it grew, but its pharmaceutical value has been far greater than that of the timber species around it. Another pharmaceutically important plant species, *Calophyllum lanigerum,* was first collected from the forests of Sarawak, but when teams returned to the original collection area for more specimens they found it had been logged and the remnant populations showed less activity (Laird and ten Kate 2002).

While global threats to biodiversity may one day affect bioprospecting, not least for pharmaceuticals (Cragg and Newman 1999; Grifo and Rosenthal 1997), there are few documented cases in which bioprospecting has been compromised by the loss of a natural community or an individual species. Given the many examples in this chapter, however, the indiscriminate loss of species or of the communities where they reside is likely to be a major threat to bioprospecting, even when their values are currently unknown or even suspected.

Many species vital for crop protection and hence large commercial revenues, for example, have been discovered in the habitat of the pest species only after intensive and prolonged research. The weevils responsible for the pest control in Australian lakes described earlier, for instance, were virtually unknown until they were needed. The same story applies to hundreds more species used to protect crops worth billions of dollars (Bellows and Fisher 1999; ten Kate and Laird 1999). Thus while the potential threat to bioprospecting through the loss of biodiversity appears very large, the actual consequences of such losses to the industry at present are very small.

10.7.2 Loss of Traditional Knowledge

Losses of traditional knowledge of biological resources in recent centuries has been well documented (see Chapter 17), and it is very likely that much local knowledge of medicines has been lost to humanity in general and to pharmaceutical prospecting in particular (Laird 2002). The current situation has been reviewed by Maffi (2001), and a growing literature on the issue (e.g., Mathooko 2001 and other publications from the International Society of Ethnobiology) documents global losses in traditional knowledge of biological sources worldwide, especially as older generations are unable, for various reasons, to pass on their wisdom to the next generations.

10.7.3 Modern Agricultural Methods

The losses of crop genetic diversity due to modern agricultural methods have been well documented (WCMC 1992; Groombridge and Jenkins 2002). In China, for example, only 10% of the 10,000 wheat varieties present in 1949 were available in the 1970s, while in Mexico only 20% of maize varieties planted in the 1930s remain and in the United States only 15–20% of apple, cabbage, maize, pea, and tomato varieties grown in the nineteenth century are available today.

The environmental effects of genetically modified crops remain unclear. But modern agricultural methods more broadly, including the removal of native vegetation, creation of larger fields, and increased use of irrigation, have resulted in biodiversity declines and losses on a large scale. In areas maintained for agricultural production, therefore, profitable bioprospecting is less likely. This may apply even to soil microorganisms, which are more specialized and less diverse in agricultural systems, although these have been shown to be restored through various agroforestry practices (Leakey 1999). Despite the lower levels of biodiversity in agricultural systems, particularly those managed under modern agricultural methods, it may be that fragments of original ecosystems in the midst of broadscale agriculture may harbor crop relatives or genetic systems of commercial value because of their adaptations to the regions or systems of interest.

10.7.4 Overharvesting

Overharvesting is a serious issue in some regions, especially when it involves plants for botanical medicines and pharmaceuticals. The situation is frequently exacerbated by poverty, especially when harvesting wild plants is both the sole source of income and the sole source of medicine for local use (Edwards 2004). Recent studies show both the dramatic effects of overharvesting, such as the declining recruitment of Brazil Nut seedlings (Peres et al. 2003), and the more subtle effects, such as the progressive shortening of available cane length in rattan populations (Siebert 2004). To avoid this kind of situation, companies such as Shaman Pharmaceuticals have instituted sustainable harvesting protocols for wild plants, such as *Croton lechleri,* a drug development candidate (King et al. 1997).

Some marine species have also been overharvested for natural products research (Farrier and Tucker 2004; Benkendorff 2002). In particular, cone shells of the molluscan family Conidae are prized for their highly variable toxins (conotoxins) for application to many areas of medicine, including pain control, cancer treatment, and microsurgery. Widespread harvesting of these animals for medical research, in addition to their collection for the sale of their shells to tourists, has led to the threatened extinction of many species throughout the tropics. Chivian et al. (2003) sum up the situation as follows: ''With up to 50,000 toxins, cone shells may contain the largest and most clinically important pharmacopoeia of any genus in nature. To lose them would be a self-destructive act of unparalleled folly.''

Food or medicinal species may be overharvested when used for export or for consumption in large urban areas (Cunningham 1993; Ferreira 1995; Malaisse 1997; MacKinnon 1998). When resources have already been degraded or reduced, as in forest systems by activities such as logging, the effects of overharvesting can be faster and more significant to local markets. While forest degradation tends to reduce the availability of medicinal resources, a few useful species thrive in the secondary growth that follows timber extraction (Shanley and Luz 2003). In South Africa, Namibia, and Botswana, wild devil's claw (*Harpagophytum procumbens*) is widely collected for its analgesic and anti-inflammatory properties, and trade data show that about 700 metric tons are collected each year. While this is actively managed in Botswana and elsewhere, and it is a protected plant across its range, the vast distances involved make enforcing regulations against overharvesting for this species extremely difficult.

The impacts of overharvesting have been recognized in many areas, and measures have been introduced to reduce levels of wild harvest. For example, Mayapple *Podophyllum* are now cultivated commercially in the United States. Another strategy, exemplified by the search of more sustainable sources of Taxol, has been to harvest from different species in different parts of the world following sustainability agreements, thereby reducing the pressure on individual populations of species.

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