

## *A New Approach to Benefit Sharing in Bioprospecting*

*E A Evans-Illidge and P T Murphy*  
*Australian Institute of Marine Science*

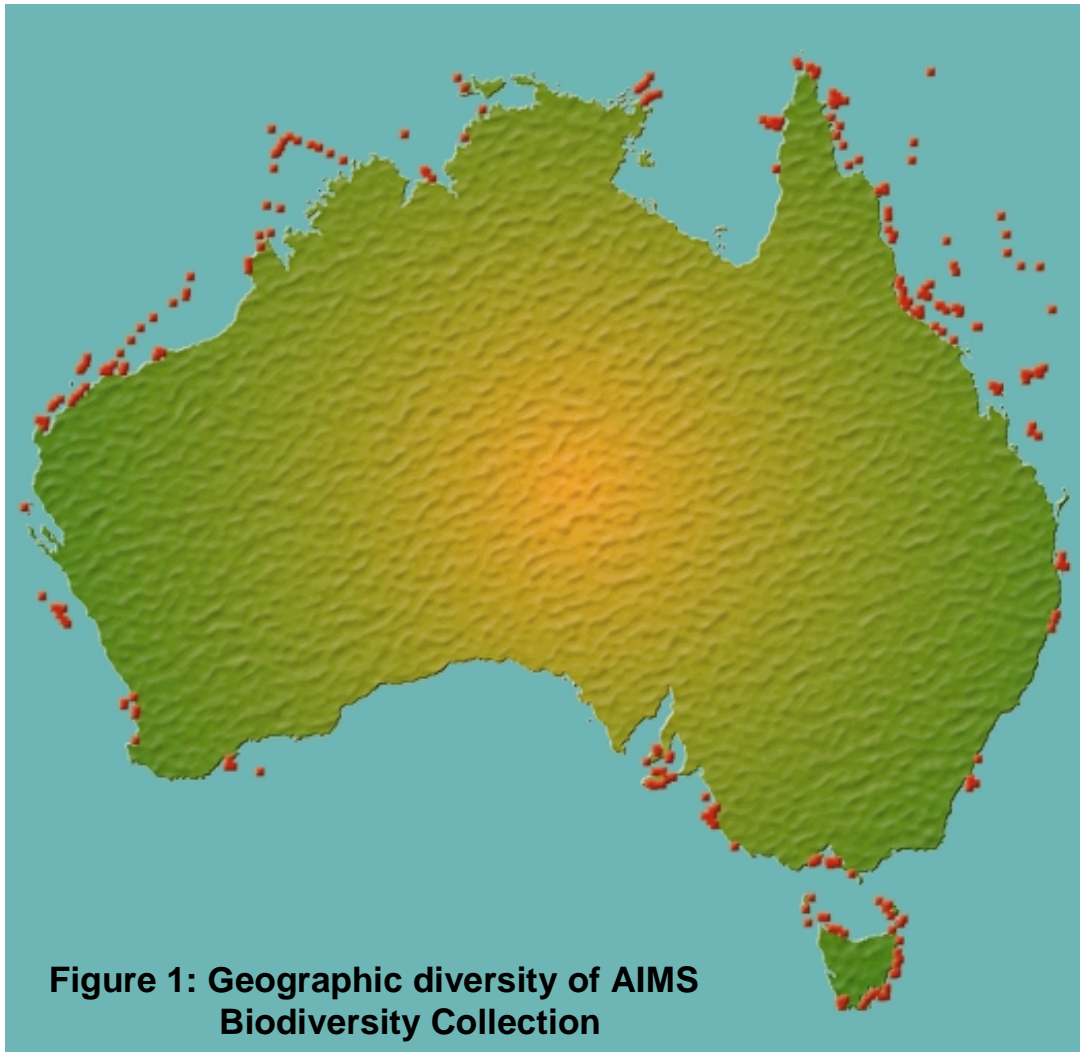
### **OVERVIEW:**

The Australian Institute of Marine Science (AIMS) is a Commonwealth Statutory Authority established by the *Australian Institute of Marine Science Act* of 1972, in recognition of a national need to manage Australia's marine environment and resources. In November 1994 Australia became responsible for a 9 million km<sup>2</sup> Exclusive Economic Zone (EEZ) which is one of the world's largest and most biodiverse ocean territories, straddling the Indo-Pacific and spanning from the tropics to Antarctica. The Marine Bioproducts Project at AIMS is therefore ideally placed to utilise the rich diversity of Australia's EEZ and to play a leading role nationally and internationally in the development of bioprospecting within the marine environment, for the benefit of Australians.

Marine organisms produce chemicals for their own use in a diverse array of functions including defence, offence and signalling. The resulting chemical arsenal evolved for these purposes is the focus of research in the Marine Bioproducts Project at AIMS. The Project is multidisciplinary, with four main functional areas: Marine Biology and Ecology, Marine Microbiology, Marine Natural Products Chemistry and Biochemistry, and Pharmacology and Toxicology. The Project is designed to provide the personnel, expertise and technology necessary to access and document Australia's marine biodiversity, and discover compounds which may be developed by industrial partners into clinically useful drugs or other beneficial products.

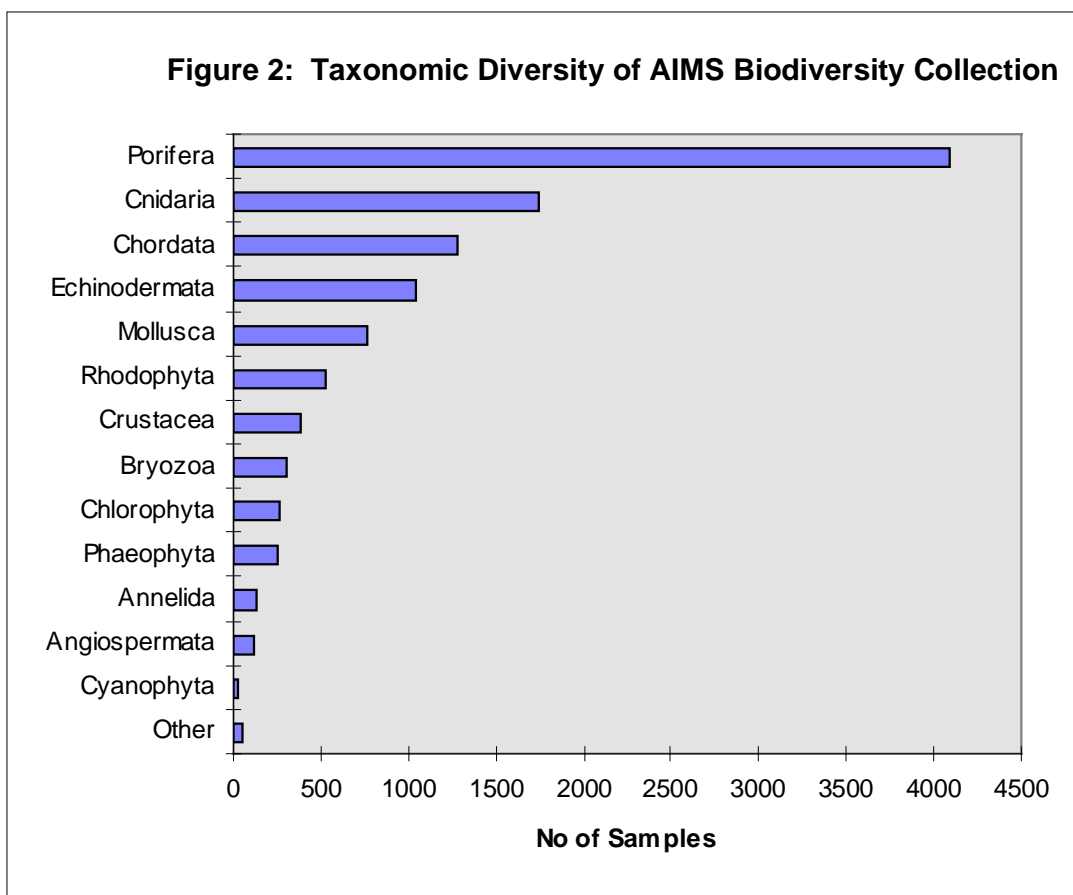
One important objective of relevance to this report is the establishment of a library of samples of biota suitable for natural products screening and systematic studies, which is representative of Australia's marine biodiversity. To date over 11 000 marine macroorganism samples have been collected from around 1500 sites around Australia, as summarised in Figures 1 and 2.

The collection is designed specifically for bioprospecting, where a relatively small quantity of a large number of organisms has been taken for general primary screening purposes. A clear distinction needs to be drawn between the bioprospecting phase and bioharvesting, where large quantities of a targeted organism are collected and wild populations are unlikely to provide an ecologically sustainable source of bioactive compounds for development. It is activities in this latter category which have received bad press over the last few years. The Marine Bioproducts Project at AIMS is well placed to investigate mariculture, culture of micro-organisms, molecular approaches and chemical synthesis as alternatives to wild bioharvesting.



Collaborations with industrial partners and other research institutions have been instrumental in the development and success of this project since its inception in 1974. It currently receives funding from AMRAD, an Australian pharmaceutical company, which was initially set up as a Victorian government initiative for development of Australian medical innovations, although it is now a public corporation. In the past, funds have also been provided by the United States National Cancer Institute (NCI). The project is presently actively seeking to diversify and establish further links in a wide range of industrial sectors including agrichemicals, fine chemicals, diagnostics and enzymes.

Despite AIMS being an emanation of the Commonwealth of Australia and its collection activities now being focused within Australian waters, certain impediments have arisen in relation to the issue of benefit sharing with various government agencies that control access. The resulting restrictions on AIMS research activities were the impetus for the development of the approach to benefit sharing outlined in the following pages.



This report aims to describe more fully the context within which AIMS undertakes its bioprospecting collection activities, and outlines the rationale and principles of the approach in which access to biodiversity could be facilitated by delaying final benefit sharing negotiations to the later and more appropriate stage where lead organisms are identified for product development. The foundation of this approach is an analysis of the bioproduct discovery and development process to distinguish components that should be regarded as high cost, high risk and essentially non-commercial research activity from those which are more focused on a commercial outcome.

***ENVIRONMENTAL CONTEXT:***

In order to make the AIMS collection representative of Australia’s marine biota, bioprospecting sites and samples are selected to span all marine invertebrate and plant phyla and as great a range of geographic and ecological gradients as possible. Historically, most sites were in shallow water accessible by SCUBA diving, largely less than 20 metres deep. Such environments were favoured because SCUBA collections are selective, and excellent *in situ* imagery and ecological data can be readily obtained. However, in recognition that most of Australia’s Ocean Territory is greater than 20 metres in depth, there has been a shift in recent years to deeper areas and the use of deployed sampling equipment such as trawl, grab and dredge gear. While representation of deep biota is patchy with gaps to be addressed in future, the AIMS collection now contains samples from depths to 800 metres.

Much of the collection contains poorly described taxa from rarely accessed areas, so data on individual species vulnerabilities are not available. However, strict collection protocols ensure minimal environmental impact and that local depletion of populations is avoided. In the case of SCUBA collecting, divers selectively pick off biota with no incidental damage, there is a small minimum material requirement of 20-400 g (often made up by only one or two individuals) and rare organisms are avoided altogether.

While deployed deep sampling equipment is less selective and by comparison more destructive, impacts are minimised through restricting the size of sampling gear. For example, 3 fathom otter trawl nets are most commonly used, a size which is barely large enough for a commercial fisher's sampling trawl. Further, collection sites are spaced so as to minimise biota overlap between sites and hence redundancy of sampling effort.

AIMS' field sample processing procedures are tailor-made to enable subsequent systematic, biological and ecological studies as well as natural product screening. In addition to material for freezing and the production of chemical extracts for screening, an appropriately preserved and taxonomically representative voucher is collected for each sample. Extensive field data is recorded, including specimen and habitat descriptions and imagery. Although initial taxonomic identifications made in the field are usually rudimentary, the material and data exist for subsequent expert taxonomic studies. The resulting collation of taxonomic material and live data of such a wide range of organisms from all around Australia has made the AIMS collection an extremely valuable resource for the documentation of Australia's marine biota.

Data records, images and vouchers for some 6500 specimens are now permanently housed at the Queensland Museum, and have been utilised in recent major revisions of groups of sponges and ascidians. In the case of marine sponges, collecting for bioprospecting has more than tripled our knowledge of their biodiversity. Over the last two decades of such activity, estimates of sponge biodiversity have gone from less than 1000 species within Australia and about 5000 worldwide, to at least 5000 and 15000 species respectively.

In addition to exploring Australia's marine macro flora and fauna diversity, the AIMS Marine Bioproducts Project is culturing and documenting a wide variety of micro-organisms. Since only an estimated 1% of microbial diversity present is culturable using standard techniques, a large proportion of the microbiology effort at AIMS is spent on the development of novel culture and fermentation procedures. Marine microbiology is a field still in relative infancy worldwide, and our work is resulting in world-first culture techniques and discoveries.

The compilation of an adequate inventory of Australia's marine resources is widely recognised as a prerequisite for an ability to manage their sustainable use and protection. Despite this acknowledgment, information on biodiversity within even our relatively well studied shallow zones is sparse while deep environments remain largely unexplored. Resources available from government funding agencies, which have historically supported this type of research, are unlikely to increase to a level which would redress this situation in the near future. It can therefore be claimed that

resource inventories produced through collections for bioprospecting are Australia's best hope of discovering and documenting its biodiversity within a useful time frame and at reduced cost to Governments.

### ***THE DOMESTIC JURISDICTIONAL CONTEXT:***

Sovereign rights to Australia's marine resources and the power to control access through legislation is vested in Australia. Through the *Coastal Waters (State Powers) Act 1980*, *Coastal Waters (Northern Territory Powers) Act 1980*, *Coastal Waters (State Title) Act 1980*, and the *Coastal Waters (Northern Territory Title) Act 1980*, title to the seabed and subsoil and legislative powers within 3 nautical miles of the territorial baseline is vested in each State and the Northern Territory.

At first glance this appears to be a simple distinction. The reality however is that domestic access to biota in Australia's Ocean Territory is controlled by a complex range of legislation through agencies at all levels of government. While a comprehensive analysis of domestic jurisdictional issues throughout Australia's marine environment is outside the scope of this report, some generalisations can be drawn.

Except in protected areas where specific legislation usually exists to control all activities within a well defined area (e.g. the *Great Barrier Reef Marine Park Act 1974* in the case of the Great Barrier Reef Marine Park), marine resources are managed by legislation principally designed for species specific fisheries. Under the *Fisheries Management Act 1991* (Commonwealth) and an inter-government agreement reached in 1979 known as the *Offshore Constitutional Settlement*, provisions were made for the Commonwealth to enter into arrangements with the states and the Northern Territory to apportion resource management roles according to the boundaries of individual fisheries rather than the 3 nautical mile line. While actual title to the seabed and subsoil is not affected by these arrangements, the result is that some activities in Commonwealth waters are subject to State or Territory legislation and vice versa, and the situation within the one location can vary depending on the species targeted or equipment used. Although this has undoubtedly streamlined fisheries licensing and management practices, it has complicated the jurisdictional setting for bioprospecting access.

## ***CURRENT RESTRICTIONS ON BIODIVERSITY ACCESS:***

The experience of the AIMS Marine Bioproducts Project suggests that, if access to marine biota is further reduced, the biodiversity available to natural products screening and development will be increasingly limited and the chance of discovering products which will bring tangible benefits to Australia will be correspondingly lowered. There is therefore a clear need for a fresh approach which facilitates access for responsible bioprospecting and increases the likelihood of commercially useful discoveries, while safeguarding the rights of appropriate authorities to claim a share in potential benefits.

A number of issues of concern are repeatedly cited by representatives of access-controlling agencies when negotiating access. These are outlined below.

Firstly, as bioprospecting is an extractive process there is undoubtedly potential for environmental impact. Concerns in this area are heightened as a result of a small number of irresponsible and well-publicised instances of large scale recollections or 'harvests'. This particular issue is always satisfactorily resolved in light of AIMS' track record of responsible bioprospecting collection and established protocols, and corresponding contributions to biodiversity documentation, in addition to the reality that the requirement for large scale recollections for drug development is extraordinary rather than the norm. Where permits are granted, they are usually conditional on collection restrictions which mirror AIMS' established protocols. Clearly, the threat of adverse environmental impact as a result of bioprospecting can be averted through consultation with the appropriate authorities and strict adherence to the resulting protocols in collection activities.

Secondly, there is an undercurrent perception that research which is not purely academic, particularly in protected areas, is unethical. This attitude persists despite government policy at all levels repeatedly asserting a requirement of research agencies such as AIMS to increase the application of research to stakeholders such as Australian industry. A full evaluation of steps required to achieve a cultural shift and resolve this issue is outside the scope of this discussion.

Perhaps the most important unresolved issue and that of direct relevance to this report is the concept of benefit sharing. The issues concerned are complex, and are often based on inaccurate perceptions of the natural products screening and bioproduct development process.

One key point of erroneous but established dogma is that pharmaceutical companies pay huge amounts of money for access to biodiversity, and that by holding back this access the quantum of "access fees" can be increased. This is not the reality. Bioprospecting is a high cost, high risk process with no guarantee of any financial returns at all. If access controlling agencies try to push the stakes even higher, industry will simply find alternative sources of chemical innovation for the bioproduct discovery process (e.g. combinatorial chemistry, microbial culture). Agencies effectively lose the opportunity to have the biodiversity in their care included in screening programs, and hence eliminate their chance of any benefits downstream.

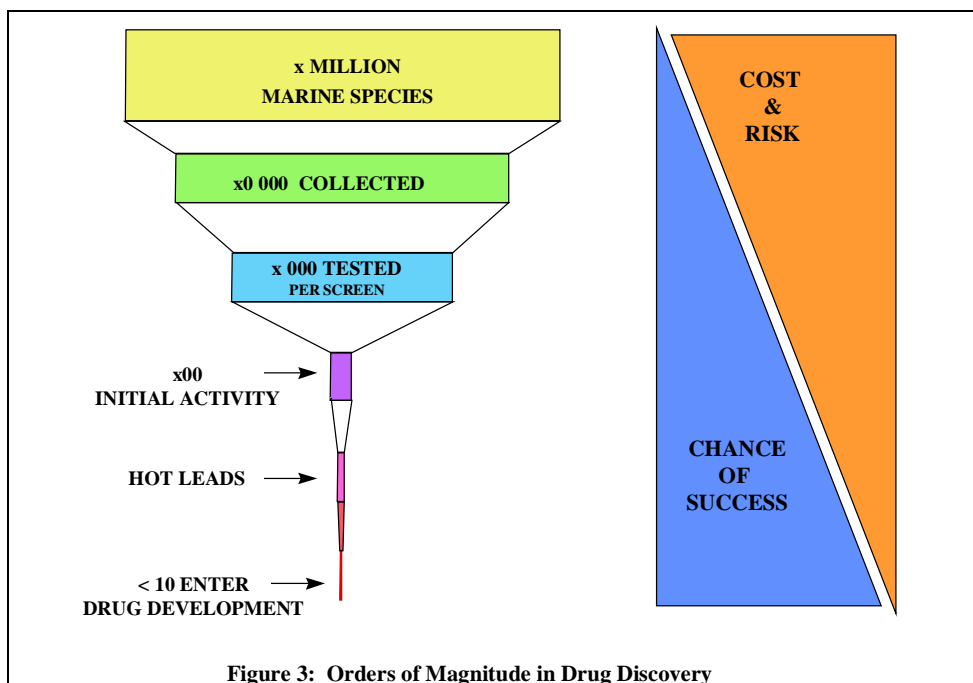
Even where the chance of a return has been raised in the case of organisms already shown to be bioactive and in need of recollection for development work to proceed, conflict over benefit sharing has hindered access to the resource. Pharmaceutical companies have been forced to explore other methods of producing the compound of interest as an alternative to accessing the original organism, or abandonment of a lead altogether.

### ***UNDERSTANDING THE BIOPRODUCT DISCOVERY PROCESS:***

If the cause of the access problem through benefit sharing conflict is based on misperceptions about aspects of bioproduct discovery and development, a key to its resolution must be a greater awareness of the total process.

The first step in drug discovery research is the acquisition of samples. What comes after organisms have been procured through collection and/or culture can be separated broadly into 'drug discovery' and 'drug development'. Activities undertaken by AIMS fit almost exclusively into the drug discovery phase, whereas most activities in the drug development phase are necessarily handled by industry partners.

The 'drug discovery' process is complex and multidisciplinary. After production of a crude extract of each sample, primary screening is the 'first pass' bioassay process. When appropriate activity is detected, various chemical techniques are employed to separate the crude extract into its components, and each component is then re-screened to identify the active fraction. This process of fractionation and re-screening is repeated again and again until the responsible active compound has been purified. As purification progresses, information about the actual structure of the compound is also gathered, and further clues are obtained through advanced spectrophotometric techniques available and being developed at AIMS. Final elucidation of the structure can be likened to patching the evidence together like the pieces of a jigsaw puzzle. Further bioassays are designed



**Figure 3: Orders of Magnitude in Drug Discovery**

to examine the mode of action of the compound and its specificity. For example, gross cytotoxicity would be a contra-indication for clinical use as an antidepressant.

As the source organism is likely to have come from a poorly described taxon, further identification work is usually required.

To complete this work there would normally be a need for an additional supply of material. A recollection with detailed taxonomy, distribution and abundance studies (macros) or scale up fermentation (micros) may be necessary. The organism's potential for mariculture, or the compound's amenability to synthetic techniques, would be concurrently assessed.

Figure 3 depicts the magnitude of sample sizes and the research effort required to produce a small number of drug development candidates, and the corresponding shift in costs and risks as the process progresses. There is no question that a primary objective of 'drug discovery' is to discover 'drug leads', or compounds which may become drugs through 'drug development'. However, in general, less than 10% of samples come through the primary screening process. At least 99% of these then drop out of the 'drug lead' race because the compound/activity combination turns out to be known, or further mechanistic studies show that the activity is not selective or not useful as a pharmaceutical. This means we are left with less than 0.1% of original samples actually becoming 'drug leads' and entering the 'drug development' phase, a process which itself has a high attrition rate. It is for this reason that natural products drug discovery has been likened to 'looking for a needle in a haystack'. It relies on a high throughput philosophy (large numbers of biodiverse samples being put through a large number of different screens) to maximise the chance of ultimately achieving just one new drug.



There is no question that the objective of drug lead production is associated with an ultimate commercial goal. However, the majority of the research undertaken produces science with no immediate commercial potential. We suggest therefore that the 'drug discovery' process, defined as the production of 'drug leads', be considered non-commercial research. 'Drug development' on the other hand should be considered as commercial research, as it is undertaken primarily by industrial partners and is focused on compounds with a higher chance of proceeding to market. As 'drug leads' are patent protected before entering 'drug development', the point of transition from non-commercial to commercial research can be well defined. The transformation of a natural product lead into a clinically-used drug will cost upwards of \$350 million dollars; most of that cost and the risk will be borne by industry.

### ***A NEW APPROACH TO BENEFIT SHARING:***

The objective of our approach is to facilitate access for bioprospecting and increase the likelihood that beneficial commercial products will be developed, while protecting the rights of the community to a share in the benefits flowing from such products.

This can be achieved by delaying final negotiations on benefit sharing with access controlling agencies until a compound reaches patent protection and the transition to commercial research. At the point of initially granting access to the resource, benefit sharing negotiations should be replaced by an agreement which commits the permittee to negotiate with the source agency should a compound originating from an organism collected under the permit proceed to commercial research.

By delaying negotiations from the high risk end of the process until there is something more tangible to negotiate over, a number of resulting factors act to enhance the likelihood of benefits flowing back to the agency. Firstly, by removing a major obstacle to access for bioprospecting, greater biodiversity will be made available to screening efforts and more potential income earning drug leads will emerge. Secondly, by inserting negotiations at a point where considerable resources have already been invested in development of the lead, industrial partners will have a forceful incentive to pursue negotiations to a resolution. Finally, because the probability of product success is much higher than at the bioprospecting end of the stakes scale and the value of potential products can be assessed, the order of magnitude of the benefit available to the source agency will be correspondingly high.

At this point, the major stakeholders in the development can be identified, as well as the major contributors of intellectual property and financial resources. The transformation of a concept of a marine organism as a source of new drugs into a commercial reality is a long and difficult process; its success will ultimately depend on a distribution of appropriate rewards commensurate with the relative contributions of the partners in the development.