NPs, Chemicals and the Environment

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Abstract and Keywords
The organisms that make Natural Products have been producing tens of thousands of different chemicals, totalling billions of tonnes every year, for billions of years. Hence, organisms have evolved to survive, indeed thrive, in the presence of these chemicals. The mechanisms evolved by organisms to cope with their chemical load are likely to be the same mechanisms used by organisms, including humans, to cope with new chemicals introduced into use by humans. This chapter shows how the subjects of toxicology and ecotoxicology can usefully be informed by the knowledge of NPs.

Keywords: Natural Products, NPs, toxicology, ecotoxicology, NP cycle

Sherlock Holmes ponders “the curious incident of the dog in the night time.” Watson, surprised, responds, “But the dog did nothing in the night time.” “That was the curious incident,” Holmes replies.
Summary
The world has never been a chemically clean place. The organisms that make NPs have been producing tens of thousands of different chemicals, totalling billions of tonnes every year, for billions of years. Hence, organisms have evolved to survive, indeed thrive, in the presence of these chemicals. The mechanisms evolved by organisms to cope with their chemical load are likely to be the same mechanisms used by organisms, including humans, to cope with new chemicals introduced into use by humans. Consequently, the subjects of toxicology and ecotoxicology can usefully be informed by the knowledge of NPs.

The fact that the world is not ‘contaminated’ by NPs to any significant extent, despite billions of years of this massive NP production, informs us that mechanisms must exist to recycle much of the carbon in NPs back into the global carbon cycle. The main routes of this NP carbon cycle must occur in microbes (which for billions of years were the only NP producers on the planet); hence, the ability of microbes to metabolise most of the substances made by humans is predictably drawing on this ancient metabolic ability. If one can understand the selection forces that could have resulted in this vital, useful and versatile metabolic capacity, it is easier to appreciate the capacity of individual organisms and ecosystems to degrade both natural and synthetic chemicals. Furthermore, by understanding the microbial capacity to degrade NPs, one can plan the best way of exploiting this capacity to target potentially harmful chemical pollutants.

The reader who is well informed about toxicology or ecotoxicology may wish to jump straight to the discussion of NPs in relation to these subjects.

The rise of public scepticism about ‘chemicals’
In most developed countries, during the past four decades of the twentieth century, many citizens were becoming increasingly concerned about ‘chemicals’ in their food, (p. 128) in water and in ‘the environment’. To the media, hence to the majority of the public, ‘chemicals’ referred to synthetic chemicals and especially to pesticides. The public concerns about the safety of the new synthetic chemicals being made and distributed around the world were not new but the
concerns resurfaced in a new form and were more widely held. What have these public concerns about synthetic chemicals got to do with NPs? To most people, there is no obvious link between NPs and concerns about chemical pollution. Indeed, even to many scientists studying pollution NPs do not seem to be relevant to the subject—as can be seen by the lack of any reference to NPs in the popular books on ecotoxicology or environmental toxicology for example. However, as explained later in this chapter, only by understanding the way in which organisms have evolved in the presence of NPs over millions of years can one understand the impact that synthetic chemicals have on the natural world.

The changing attitudes to pesticides and pharmaceutical drugs

The acceptance of the government's role in protecting the public from hazards

Individuals had been aware of chemical pollution in all industrial countries since the nineteenth century, especially in areas near gas works, smelting plants, chemical factories, oil refineries or mines. In general, the poor and politically disenfranchised suffered most. The rich used their wealth to move to cleaner areas, in the same way they had for centuries fled areas contaminated by human and animal waste. In Europe, however, the replacement of numerous small local manufacturers throughout the country by a few huge factories in a small number of rapidly expanding cities increased the chances that significant numbers in the population would be exposed to harmful concentrations of toxic chemicals. Improving scientific knowledge, changing social attitudes and a broadening political franchise eventually allowed these growing problems to be recognised and addressed. The statutory control of the exposure of individuals to toxic chemicals in the workplace (e.g., the notorious effects of white and yellow phosphorous used in the manufacture of matches) began in the late nineteenth century and subsequently planning laws and emissions controls gave protection to whole communities that had previously been exposed to pollution.

These nineteenth century and early twentieth century great successes in improving the health of citizens, by the elimination or control of hazards, had a profound effect on the thinking of the public about risk. Good government, at national and local level, could increase the chances of individuals living a long and healthy life. It was the action of local or national
governments, not individual behaviour, that had been most effective in improving the well-being of the average citizen, especially the poorer citizen. There was a growing consensus that it was the duty of government to protect citizens from hazards that the citizen could not control by their own individual behaviour. So, once (p.129)

safe drinking water had been made available to most citizens, attention was turned to food safety. In the nineteenth century, concerns about ‘chemicals’ in food were related to adulteration (reducing food quality by substituting low food value material) rather than the adverse effects that the minor toxic contamination might have on the consumers. There were some well-known examples of the chemical contamination of food, but it was not synthetic chemicals that were the problem but the contamination of grain with microbial NPs. The alkaloid ergot (Figure 6.1), produced by the ascomycete fungus *Claviceps purpurea*, induces hallucinations similar to those produced by the psychotic drug LSD (lysergic acid), it can induce abortions and can constrict blood capillaries to the extent that lethal gangrene may result from a lack of blood circulation. Rye, a major grain in northern Europe, was the grain that was most at-risk of ergot contamination but government-led control measures (improved analytical methods, good crop husbandry and improved processing) eliminated the problem. However, the contamination of food with toxic NPs remains a problem. Aflatoxin, produced by the mould *Aspergillus flavus*, can contaminate some nuts (especially peanut and Brazil nuts) and is converted by humans to a very powerful mutagenic chemical. Government-led food quality standards now stop the sale of aflatoxin-contaminated foods in many countries and even some bird foods are now advertised as being free of the toxin.

*Figure 6.1. Representatives of the Aflatoxin and Ergot alkaloid families.*
The rising concern about toxic chemicals in foods

It was soon after the widespread introduction of chemicals into agricultural use in the early part of the twentieth century (to kill insect pests, to control fungal diseases, to kill weeds and to rid animals of parasites) that public concern about the use of these highly poisonous chemicals in food production began to grow. These concerns now seem legitimate because the first generation of widely used agricultural chemicals included the salts of some heavy metals (arsenic, lead and mercury) that were very toxic\(^{(p.130)}\) to many organisms. There were also some toxic NPs (e.g., nicotine) used to control insects. The safe use of such non-selective toxic chemicals relied on the targeted application of the toxin directly to the insect or fungus in such a way that the harvested product was uncontaminated at the time of harvest. Clearly, this was relatively easy in the case of grain crops (where the grain developed well away from the leaves that might have needed chemical protection earlier in the season). However, this was very hard to achieve when the grower was trying to protect a product that the consumer would consume (e.g., apple, lettuce leaf, tomato, etc.), which was also the object of attack by the insect or fungus. Thus, the protection of the consumer relied heavily on the proper use of the poison by the user—always a recipe for disaster given the uncertainty of human behaviour. How could the public be sure that growers were not allowing poisonous residues to remain on the foods going to market? Recognising the potential for serious problems, in the early twentieth century, governments in many countries enacted laws in response to rising public concern. However, the seeds of doubt about the safety of agrochemicals had been sown in the minds of the consumers—the public realised that laws which rely on the unpolicied compliance of standards offer only limited protection. Public doubts were not helped by many lurid tales in popular fiction where murderers were often caught using rat poison, weed killer or some other noxious chemical, purchased legitimately, to send their victims to the grave.

The rising acceptance of the use of pharmaceutical chemicals

At around this time, in the first decade of the twentieth century, the German microbiologist Paul Ehrlich (1854–1915) showed that some synthetic chemicals had a highly selective toxic action on some organisms. Ehrlich took his inspiration from the accumulating evidence that some of the increasingly
available synthetic dyes (see Chapters 2 and 8) stained only some natural substances. Some dyes only stained cotton but not wool for example. Microscopists had long used dyes to aid the visualisation of cells and organelles, using the synthetic dyes to identify cell types because the walls of some types of plant cell would associate with certain coloured dyes and not others (Figure 6.2 and read Chapter 9 for a possible explanation of why this should be so). Ehrlich was particularly impressed by the fact that synthetic chemical dyes stained some microbes and not others\(^1\) and by the fact that certain parasites took up dyes easily. Ehrlich reasoned that it would be expected that organisms, tissues or organelles that accumulated dyes would in effect be exposed to those chemicals at higher concentrations than those structures that did not take up the dyes. Given that he knew that some dyes were toxic at high doses, he reasoned that selective toxicity might be possible. By screening\(^2\) a large number of dyes, Ehrlich showed that it was possible to find a chemical that killed a parasite without killing the host.\(^3\) The important concept of ‘selective toxicity’ was verified and the large-scale screening of large collections of chemicals, in the search for the rare chemical that might kill one type of cell and not another, was adopted by many companies, companies that eventually became part of the huge pharmaceutical industry (p.131)

(see Chapter 7 for further information on the developments of Ehrlich's ideas and the pharmaceutical industry).

It was to take decades before Ehrlich's ideas on selective toxicity were to influence the growing agrochemical and veterinary industries. By the 1930s, however, a number of companies soon found synthetic
chemicals that would selectively kill plant pathogenic fungi or would control the insect pests of plants and animals. The 1930s was also the period of discovery of some extremely highly selective pharmaceutical drugs (see also Chapter 7). The synthetic sulphanilamide antibacterial substances came into use at around this time and a few years later penicillin (an NP) became available and was soon hailed as the first wonder drug. These advances began to reassure the public that a person could ingest a chemical without any expectation of an adverse effect on themselves but with a devastation effect on some organism within them. The public began to take the concept of selective toxicity to heart—clearly, not all chemicals were harmful.

The mid-twentieth century enthusiasm for synthetic chemicals DDT

It was the selective toxicity of the insecticide DDT that was destined to have a most profound effect on attitudes to chemical safety. DDT was a chemical that had first been synthesised decades before the Swiss chemist Müller discovered its potent insecticidal action in the late 1930s. What was so remarkable about DDT was its selectivity. Even in extremely small doses, it was lethal to many species of insect yet it was remarkably non-toxic to humans even at quite high doses (Figure 6.3). The manufacture of DDT is (p.132)
relatively simple; hence, the chemical could be made cheaply in large quantities. Huge amounts of DDT were used in the Second World War to kill insect parasites (lice had been a very serious problem to soldiers and refugees during the First World War) and to control insect-borne diseases (malaria could debilitate an army). Such was the selectivity of DDT that refugees and soldiers could be casually dusted with DDT powder, during which time they would inevitably ingest particles. The persistence of DDT in clothing was regarded as a positive attribute because it gave lasting protection against re-infestation.

The impact of the introduction of DDT in reducing the death rate from malaria, caused by a mosquito-borne parasite, was especially dramatic. It has been claimed that by reducing the huge death tolls from malaria, DDT saved more lives than penicillin. DDT was cheap, effective and its persistence gave it a very long residual effect which allowed it to give a prolonged control of insects in houses when DDT was sprayed onto the walls of houses or even incorporated into wall paint. The attitude of most consumers to these new insecticides was transformed. In the early 1950s, the public were delighted to

**Figure 6.3.** The LD$_{50}$ is the concentration of a substance that kills 50% of a test population of organisms. It is a useful measure to compare the toxicity of different substances but it is a very controversial measurement when applied to mammals because of the suffering caused to the animals used to gain the data. Note that if the LD$_{50}$ dose is increased by a factor of 10, nearly 100% of the population will die and if the concentration of the substance drops to one-tenth of the LD$_{50}$ then only a very small percentage will die. The notorious insecticide DDT has an LD$_{50}$ of 150–300 mg kg$^{-1}$ for rats, 1 g kg$^{-1}$ for goats, 2 g kg$^{-1}$ for ducks but <0.1 mg kg$^{-1}$ for some aquatic invertebrates.
use DDT freely around their homes and gardens—the sticky fly paper in the kitchen was replaced by the insecticide sprayer in millions of homes.

DDT was not the only synthetic chemical to find a use in private and commercial gardens. Plant physiologists in the 1930s had accidentally discovered a way of selectively killing weeds in cereal crops (the dominant source of food for humans—wheat, barley, maize and rice). The plant physiologists interested in how plants controlled their growth had discovered a plant hormone—auxin (indole-3-acetic acid). Chemists soon found that, not only was it easy to make this compound, but they could also easily make (p.133) hundreds of chemicals that were chemically related and structurally similar. A few of these auxin analogues were as biologically active as authentic auxin and these shared with auxin the remarkable property that when applied to a young cereal crop, the dose that had no effect on the cereal plants killed the majority of the broadleaved weeds. By the late 1940s, farmers in most developed countries were spraying their cereal crops in late spring every year with auxin analogues (the most widely used were 2,4-D and MCPA, both chemicals still being in use today). Weeds were not only a problem in cereal fields but also in grassland (cereals are grasses), so dairy farmers also began to use them. Given that grasses were also sown over large areas in urban settings (on golf courses, soccer pitches, cricket grounds, bowl greens, city parks and private gardens) these same weed killers were widely used in such settings. Families, and their pets, would use the lawns immediately after spraying without concern. New fungicides also became available to horticulturists and gardeners at this time and these ‘safe’ chemicals would be sprayed on garden flowers, vegetables or fruits in the garden, some of the latter would be consumed within days without concern.
Silent Spring
The public's benevolent attitude to chemicals was to change abruptly when the book *Silent Spring* was published in 1962. This remarkably effective polemic by Rachel Carson argued that the widespread use of pesticides was responsible for a dramatic decline in wildlife. The title of the book was a brilliant emotional hook for the public, despite the fact that most people rarely heard the dawn chorus or even knew it existed. For the pesticide industry, *Silent Spring* was a public relations disaster. Birds have a special place in the minds of humans. Many humans feed birds in their garden or take their children to feed birds in a local park. In the United Kingdom, The Royal Society for the Protection of Birds (which has the largest subscription membership of any in the United Kingdom) has the title which suggests that birds deserve the protection of the monarch. One theme running through Rachel Carson's book was that it is the insidious nature of pesticides that allowed them to be widely adopted without early evident harm. If prolonged exposure to small doses of synthetic chemicals could kill birds, maybe they could harm humans in the long term. The decline in iconic species like the birds of prey struck a special chord with the public. If the top predators were especially vulnerable, maybe humans, who are also near the top of the food chain, should also worry. A number of scientists had already identified some characteristics of one group of pesticides, the organochlorines (DDT, aldrin, dieldrin, etc.), that suggested that these chemicals might build up in tissues of non-target species after prolonged exposure to very low doses. Maybe the safety testing of new pesticides in the 1950s, testing which concentrated on the effects of acute (short-term) exposure, did not adequately reveal the chronic (long-term) effects? The organochlorines were characterised by high fat solubility which enabled them to penetrate the waxy insect cuticle. They also had great chemical stability which gave them the very long persistence much valued for some uses. However, these properties when combined also caused the organochlorines to accumulate in the fatty cells of any organism exposed to them and to persist for long periods. The result of these properties was that a small organism swimming in water containing a minute concentration of DDT would have a DDT concentration in its body that exceeded that in the water. A predator organism that consumed that little organism would accumulate the ingested DDT in its fat cells every time it fed.
As one progressed up the food chain, the concentration of DDT was found to rise remarkably and the top predators would experience the highest doses. The public were soon alarmed that the same chemicals might be accumulating in humans.

Just at this time, the method of analysing samples for pesticide residues was revolutionised by the invention of the electron capture gas liquid chromatograph (invented by James Lovelock of the Gaia hypothesis fame). This instrument was especially good at detecting molecules containing chlorine; hence, the analysis of the organochlorines suddenly became something that could be carried out conveniently with huge sensitivity. Soon, evidence was published revealing the presence of organochlorine chemicals in samples of bird tissues, bird eggs, cattle, milk and even in humans milk—the latter hitting yet another button leading to human alarm. The organochlorine contamination was found to be worldwide. Even organisms in remote ecosystems such as penguins were found to contain organochlorines. Despite the fact that there was no recorded human death from unintended DDT exposure, the seeds had been sown for distrust of pesticides in particular but synthetic chemicals in general.

**Thalidomide**

To compound this increasing scepticism about the use of synthetic chemicals, the pharmaceutical industry gave the world Thalidomide. In the late 1950s and early 1960s, Thalidomide was prescribed to large numbers of pregnant women in Europe, Canada and Australia to treat morning sickness. Despite very extensive safety testing of the drug before it was approved for use, it caused horrific deformities in a small proportion of the children born to women taking this drug. Inevitably, an increasing number of people began to note that scientists had been unable to protect wildlife, or indeed humans, from the adverse effect of synthetic chemicals. These problems had arisen despite the large number of scientific studies undertaken to address the issue of the safety of all such chemicals. The public scepticism of the skills and motivations of scientists grew.
The rising public concern
If scientists could be wrong about such widely used chemicals, and they could not foresee the very fundamental problems associated with particular chemicals, why should the public be reassured that other chemicals to which they were exposed were safe? Journalists had long known that scare stories help to sell newspapers; consequently, there would be few citizens in most developed countries that did not know of the debate about the safety of pesticides and pharmaceutical drugs by the 1970s. The concerns of the public were soon drawn upon by new political parties, such as the Greens, and some of the newly powerful Non-Governmental Organisations (NGOs). These groups soon became very effective lobbying organisations. Arguing that there would be a public benefit from a reduction in pesticide use, improved safety testing and more extensive environmental impact studies, Greenpeace, Friends of the Earth, WWF and their equivalents elsewhere gained wide support. These organisations were soon trusted more by large sections of the public than industry and government scientists. Indeed, the NGOs, which rose to power partly by questioning the safety of chemicals in the environment helped shape the wider political agenda in the last decades of the twentieth century so that environmentalism became part of the political and corporate mainstream.

The political, scientific and industrial responses
The sensitive antennae of politicians began to pick up signals that voters wanted a tighter regulation of the chemical, agrochemical and pharmaceutical industries. As usual when the public show concern about an issue, politicians are always ready to demonstrate their own concern by using public money to fund scientists to research the issues related to the problem. In the 1950s, it was toxicologists, studying the direct effects of chemicals on individuals in a laboratory, who had dominated chemical safety studies. Attention now turned to the effects, direct and indirect, of chemicals on populations. The growth of ecology as a subject at this time was greatly aided by new public funds directed to universities, government research institutes and government agencies to address these perceived problems with the use of chemicals. Inevitably, once these new academic disciplines had been established, the new breed of scientists dug deep to find problems as well as to suggest ways of resolving them. The funding of this research
depended on the subject being kept ‘live’ and the popular media were ever ready to exploit any potential scare story that emerged from the scientific research.

**Regulation**

One of the most significant political responses to the public concern about chemicals, stimulated by Rachel Carson's book, was the establishment of the United States Environmental Protection Agency (EPA) in 1972. The EPA was very significant even beyond the shores of the United States. Because the United States was the largest single market in the world for the chemical industry, if a chemical manufacturer outside the United States wanted to access the huge US market, they had to comply with EPA demands. Furthermore, the agrochemical industry had already begun a process of consolidation in the 1960s and multinationals were growing rapidly. When US demands were made on the multinationals in order for them to sell into the US market, those demands would influence the multinational chemical and agrochemical companies worldwide. The EPA established a much more rigorous system of judging whether a chemical should be allowed on to the market (Table 6.1). Not only was much more data required for approval in terms of the toxicological properties of any individual chemical, but for the first time the environmental impact of the use of any chemical had to be fully considered.  

(p.136)

**Table 6.1. In the early 1960s the increasing public concern about the safety of pesticides resulted in governments in the developed world requiring manufacturers to provide extra detailed results of more extensive safety testing of new pesticides.**

<table>
<thead>
<tr>
<th>1950</th>
<th>1965</th>
<th>1980</th>
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<tbody>
<tr>
<td>Toxicology</td>
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<tr>
<td>Acute toxicity</td>
<td>Acute toxicity</td>
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<tr>
<td>(LD$_{50}$)</td>
<td>(LD$_{50}$)</td>
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<tr>
<td>30–90 d rat feeding</td>
<td>90 d rat feeding</td>
<td>90 d dog feeding</td>
</tr>
<tr>
<td></td>
<td>2 y rat feeding</td>
<td>2 y dog feeding</td>
</tr>
<tr>
<td></td>
<td>Reproduction in 3 rat generations</td>
<td></td>
</tr>
</tbody>
</table>
Industrial consolidation
Throughout the last two decades of the twentieth century and the early years of the new millennium, industrial consolidation continued in both the agrochemical industry and the pharmaceutical industry. A number of the major agrochemical companies had diversified into the pharmaceutical market, often via explorations of the veterinary drug market. However, in general, the exploitation of the principles of selective toxicity in the pharmaceutical industry was more profitable than the use of the same principles in the agrochemical industry. Consequently, after some mergers there was sometimes a realignment of the new multinational into two companies, one a pharmaceutical company and the other one an agrochemical company. It is possible that part of the motivation for this was to protect successful pharmaceutical brands from any adverse publicity that might come from the still existent adverse public attitudes to agrochemicals (and later GM crops because agrochemical

<table>
<thead>
<tr>
<th></th>
<th>1950</th>
<th>1965</th>
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</tr>
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<tbody>
<tr>
<td>Metabolism</td>
<td>None</td>
<td>Rat</td>
<td>Rat and dog Plants</td>
</tr>
<tr>
<td>Residues</td>
<td>Food crops 1 ppm</td>
<td>Food crops 0.1 ppm Meat 0.1 ppm Milk 0.1 ppm</td>
<td>Food crops 0.01 ppm Meat 0.1 ppm Milk 0.005 ppm</td>
</tr>
<tr>
<td>Ecology</td>
<td>None</td>
<td>None</td>
<td>Environmental stability Environmental movement Accumulation Total effects on all non-target species</td>
</tr>
</tbody>
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Source: Taken from Green, Hartley and West (1987).
companies had increasingly taken over the seed supply businesses).
The broader picture

Although public concern was focused on pesticides, and to a lesser extent on pharmaceutical products, some other types of products came to the attention of the public, hence alerting them to the fact that they were exposed to many chemicals.

(p.137) Concern about food additives became so significant that food producers managed to seduce consumers with the prominent labels proclaiming ‘free from artificial flavours’ or ‘no artificial colouring’. Such additives were blamed by some as being responsible for criminal, disruptive or violent behaviour of children. Food labelling, either under voluntary codes or by law, was introduced in response to such concerns. In Europe, the adoption of E numbers to identify commonly used food additives supposedly helped consumers make informed choices (or possibly helped alleviate some public fears).

By the end of the twentieth century, 30 years of increased safety testing, environmental monitoring and regulation had not entirely allayed public fears. The cost of some regulations was very considerable and in some instances these controls were based more on appeasing public concern than on scientific evidence.\textsuperscript{10} For example, the European Union Drinking Water Directive addressed the issue of pesticide residues in drinking water. The European countries, along with many other countries, had previously enacted laws that imposed limits on the concentration of pesticides in drinking water, these limits being based on toxicological evidence. Choosing a figure for the limit for any chemical cannot be an exact science because the limit must always be set well below the concentration that clearly shows a statistically significant effect. This is a difficulty that few consumers and most politicians understand. The public and politicians want scientists to demonstrate that a chemical is safe—which is impossible because experiments can only show statistically meaningful positive effects. Practically, the best a scientist can do is to establish a concentration of a chemical that, under the conditions studied, will cause harm and then extrapolate from that information to predict a concentration that will cause no effect. Because the Law of Mass Action (as explained in Chapter 5) shows that the relationship between dose and response is log-linear (e.g., the dose of the applied chemicals has to increase by a factor of 10 to increase the effect by a factor of 2), a commonly accepted margin for safety is that it...
should be safe to consume 1/100 of the dose that is known from experimental studies to cause no measurable effect (Figure 6.3). However, such safety margins are extrapolations and are clearly based on many assumptions. Maybe humans are more sensitive than the species used to gain the toxicological data. Maybe laboratory bred strains of an organism show a narrower range of sensitivity than would be found in a human population. This is quite possible given that, in order to aid statistical inference, laboratory strains of organisms are often highly inbred, fed very uniform diets and kept free of disease and stress in order to produce a necessary uniformity. Maybe long-term exposure to low levels of the chemical will only reveal adverse effects after several years—humans live for decades, yet rodents, commonly used in laboratory studies, live for months. So, is the 100-fold safety margin sufficient? The response of the politicians to these dilemmas was not to side with the scientists who had spent decades trying to understand the possible effects of these chemicals. Instead, the European Union (EU) politicians decided that there should be no pesticides in drinking water. This simplistic idea, popular with voters, was clearly scientifically problematic, indeed it was unachievable. If one allows pesticides to be made and sold, they are inevitably going to enter drinking water. A farmer applying a fungicide to a field, a local authority using herbicides on footpaths, a timber treatment company treating woodworm in homes, indeed the gardener spraying their lawn or the pet owner throwing out their unused pet flea control agent are all opening up routes for their chemical to enter local water courses. Eventually, some of those chemicals will reach someone’s drinking water, albeit in minute amounts. A very large number of studies have shown that chemicals are distributed globally by many different routes and even if one country tries to reduce the pesticide use within its borders, residues will still be found albeit at extremely low levels. Thus, the EU passed a law that aimed to achieve the impossible. However, another practical problem faced EU legislators, how could it be shown that a sample of drinking water contained no pesticide? Clearly by analysing water samples one can look for the presence of a chemical but how little of any pesticide can one detect? Analytical chemists advised that methods were available that could detect 0.1 μg L⁻¹ of any pesticide; hence, it was practical to use that concentration as the legal limit which must not be exceeded. So, we have a fine example
of how politicians will happily ignore scientists when it suits them, yet at other times hide behind ‘scientific opinion’. In this case, trying to achieve the impossible, EU legislators adopted a standard that was based on the wrong piece of science. The huge amounts of toxicological evidence and expertise that had been gained over the decades were simply put aside. The resulting cost of this political expediency was huge. In the UK alone, it was estimated that the water industry incurred capital costs in excess of £1.5 billion and annual running costs of £100 million to reduce the level of pesticides in drinking water from concentrations that were regarded by most experts as presenting no significant risk to levels that were even less of a risk. What the law did not achieve, and could not achieve, was to eliminate pesticides from drinking water!¹¹

The EU Drinking Water Directive has been discussed in such detail because it demonstrates how a few notorious examples of chemicals causing environmental and human welfare problems grew into such a general concern that legislators were ready to enact unsound laws, at huge expense to protect the public from risks which were minute compared to many other risks that the public accept. (The wily politicians also kept quiet about the fact that they have ignored their mantra of ‘the polluter pays’ because in this case the consumer was paying, not the farmers or agrochemical industry!)
NPs—what they can tell us about chemical pollution

Once the public had their attention drawn to the chemicals to which they were being exposed, it is hardly surprising that they found plenty to worry about. There are 75,000–90,000 synthetic chemicals in use, many of which have never been a subject of intensive toxicological testing. Even fewer have been subject to thorough environmental impact assessments. These facts were emphasised to the public, especially by some of the NGOs. Virtually, the only time members of the public heard or read about individual chemicals in the media was when they were mentioned as part of scare stories—pesticides in food, contaminants in tap and bottled water, side effects of drugs and so forth. Yet many people willingly expose themselves to hundreds of artificial chemicals throughout their day—starting with a highly scented, pigmented shower gel, hair conditioner, deodorant, cosmetics, dressing in polyester clothing recently washed in a detergent and softened with a fabric softener, drinking an artificially sweetened cola in a plastic bottle, chewing a fruit flavoured sweet, washing the crockery in detergent and so forth. Daily, hundreds of other synthetic chemicals are also likely to enter the body simply because it is inevitable that chemicals that are in use in society will always get into the environment; consequently, it is inevitable that they will be found in foods, water and homes.

It was inevitable that once the public had learned that chemicals could be dangerous, should anyone suggest that a specific chemical, or indeed even an unknown chemical, might be the cause of some newly perceived problem, citizens would look at chemicals as guilty until proved innocent. One might wonder why at the end of the twentieth century, when there are more people than ever who have had a scientific education, that the public has a sceptical attitude to chemicals. Given that the high standard of living enjoyed by most citizens of the developed world comes partly from the widespread use of chemicals, why is the public so distrustful of them? Why have scientists been unable to engage the public in a more helpful debate about the risk that chemicals in the environment pose to the average citizen? Scientists have not managed to give the average citizen enough understanding of the simple principles, outlined in the earlier chapters, to enable each citizen to make sound judgements about the risks that chemicals in their environment might pose. Indeed, so little confidence does the public have in scientific evaluations
of chemical risks that the public are now quite prepared to ignore scientific evaluations on any topic—MMR, BSE, etc. Maybe if the arguments about chemicals in our environment were built on new foundations, the public might be better served.

Why an understanding of the evolution of NPs should underpin our attitudes to synthetic chemicals
The world has never been a chemically clean place

There seems to be an unstated assumption, held by many, that the world was a chemically clean place until humans began to manufacture chemicals industrially. This is completely wrong. Plants and microbes have been making maybe 500,000 different NPs for hundreds of millions of years and they continue to do so. Not only do organisms make a very large number of complex chemicals, they make them in very large amounts. It is hard to estimate how great this flow of carbon into NPs might be, but if only 1% of carbon fixed annually by plants (estimated to be 100 billion tonnes per annum) was converted into NPs, a total of in excess of a billion tonnes of NPs are made by organisms each year.\(^{12}\) This figure suggests that biological chemical production greatly exceeds industrial chemical manufacture by a very large margin. Thus, humans did not begin something new when they started making and releasing chemicals, they (p.140) simply contributed to a series of processes that have operated as part of the natural world throughout evolutionary time. Humans are now contributing very significantly to the quantity of chemicals being made annually and they have added to the overall chemical diversity but they are still minor players. Once one accepts the simple fact that humans are but the latest chemists in the world, the contributions that humans make to global chemistry and the way in which synthetic chemicals might have an effect on the world can be viewed with greater clarity.

Recognising that the world has contained hundreds of thousands of chemicals for billions of years, it becomes clear that most organisms must have evolved in a chemically complex environment. Some of the NPs are very potent poisons or have dramatic physiological effects on some organisms. Consequently, organisms will have evolved to cope with the chemical environment in which they have lived. It is predictable that organisms will have evolved mechanisms that enable them to survive, or thrive, in the presence of a mixture of chemicals, some of which may be harmful to them if accumulated or ingested in large enough doses. In the analogous way that individual organisms can survive very harsh physical environments, sometimes with remarkable morphological or behavioural adaptations, so it is to be expected that organisms will have evolved to cope with their own chemical environments. Just as most people from their
own experience as animals can identify a few general principles that aid the survival of animals in harsh environments, so it is possible to identify a few general principles that will guide our consideration as to how organisms have evolved to cope with chemicals they encounter, willingly or unwillingly. It is to be expected that examples will be found where organisms

- avoid a particular chemical;
- are attracted to a particular chemical;
- possess mechanisms to reduce the concentration of a chemical in their bodies;
- possess mechanisms to enhance the retention of a particular chemical;
- have adapted to the presence of a particular chemical or group of chemicals; and
- have adapted to exploit a chemical that they do not make but have access to.

In other words, most organisms will have evolved to survive with chemical diversity in their environment. An organism exposed to a new natural or synthetic chemical will simply have one extra chemical in its environment. For reasons discussed in Chapter 5, the chances are extremely small that the new chemical will possess the particular properties that endow it with the potential to reduce the fitness of the organism. For billions of years, individuals of all species will, at intervals, have been exposed to a chemical that they have not encountered before. This will be a situation that might have happened many times in the lifetime of some individuals. It is certainly a circumstance that will have arisen many times in the recent evolutionary history of many species when species have increased their habitat range with the result that they inevitably encounter NPs that are novel to them. In other words, being exposed to new chemicals is a normal part of life. A good example of this fact comes from humans. Humans have been very (p. 141) successful at exploiting plants to add nutrition and interest to their diet. Every new plant added to the human diet contains hundred of NPs and most humans can ingest the new mixture of chemicals contained in novel food plants without ill effect. So, how do organisms, including humans, cope with new chemicals in their environment or diet?

How have organisms evolved to live in the chemically complex world?

Avoiding a chemical
Location
Most organisms avoid most of the NPs in the world simply by living in particular places. Because most NPs are made only by a very limited number of species and because each species is usually only found in limited geographical area, the spatial distribution of each NP is usually very limited. The adaptation of any one species to a particular habitat limits the number of NP-producing species that will be contributing to any individual's chemical load. However, the more one species moves around, adapts to new locations and adopts new diets, the greater the range of NPs that species will encounter. Humans as a species must encounter many more NPs than most species (although goats have a formidable reputation as being able to eat anything).

Choice
Organisms that can move can also make behavioural choices to influence the type and magnitude of chemical exposure. The fact that many (most?) organisms, capable of movement, possess an ability to detect individual chemicals (using mechanisms analogous to those that humans call taste and smell), suggests that the ability to select or reject environments on the basis of chemical information, or to choose particular foods in that environment, was highly beneficial. Human experience shows that individuals make food choices on the basis of smell and taste, both largely governed by NPs. The co-evolution of insects and plants provides a further example of limitation of exposure by choice. Each specialist insect species limits its exposure to the number of NPs within its ecosystem and such insects have evolved in a chemical world that is less diverse than the chemical world of the local area, much less diverse than the chemical diversity of the country in which they reside and very, very much less than the chemical diversity of the world.

Reducing the concentration of a chemical
Even an organism reducing the chemical diversity and chemical load by selecting its food sources will still be exposed to some NPs. Without some mechanism to limit the concentration of these chemicals in the cells, the organisms might accumulate sufficiently high concentrations of some chemicals for those substances to have physiological effects on the organism and reduce its fitness. The Law of Mass Action (see Chapter 5) (p.142) tells us that if an organism can keep the concentration of any potentially deleterious chemical below the threshold needed to cause an adverse effect, it will gain fitness. Surviving the ingestion of a toxic chemical is not about totally eliminating the potential toxin; it is about reducing the concentration of the substance to below a toxic level. The fitness gains of never needlessly eliminating a chemical will be significant. A mechanism that could potentially totally eliminate a specific chemical would not enhance fitness but might increase the costs; hence, such mechanisms would not be favoured by evolution.

**Degradation and excretion**

It is too simplistic to think that the metabolism of exogenous chemicals, whether natural or synthetic, by an organism is a way that the organism reduces the risk of exposure to an excess of any chemical. Consider the example of the human eating a pizza topped with tomato, green peppers, broccoli, mushrooms, capers and olives. Each bite will introduce a very complex mixture of NPs into the body—hundreds of exotic chemicals will enter the bloodstream. Each chemical will have properties that will govern its potential for harm. A very few of the chemicals might be quite toxic if given in larger doses but the concentrations achieved after eating the pizza will not be toxic—otherwise, humans would not eat them. A few of the chemicals might possess no potent biomolecular activity but might be converted by the pizza eater's degradative enzymes into new chemicals which possess much greater potential for harm. The unpredictability of the chemical mixture being encountered, the unpredictability of the properties of the chemicals being ingested, the unpredictability of the new chemical made as a result of the action of the degradative enzymes, these are all potential problems that the organism must have evolved to cope with. It seems unlikely that organisms with a varied diet, rich in NPs, will have evolved to possess enzymes targeted at each of the major NPs. Given the degree of unpredictability that ingesting NPs brings, it
seems possible that evolution has selected individuals that simply possesses the ability to keep the concentration of exogenous chemicals as low as possible, using generic mechanisms that are largely non-selective. Any organism with an excretion system possesses a route to dispose of chemicals; hence, it is predictable that mechanisms to direct ingested chemicals to that disposal route might have been selected. A plausible explanation is that organisms faced with a varying diet containing a mixture of compounds of unknown biological activity might be expected to have evolved mechanisms to rid the body of a wide range of substances irrespective of the biological or biomolecular activity of each substance. For example in mammals, most water-soluble chemicals ingested will automatically be diluted in the body simply because of the high water content of the body; furthermore, any soluble chemical will be excreted via urine. Consequently, there might be a rather limited selection pressure on organisms to evolve enzymes especially aimed at degrading most water-soluble NPs—dilution and loss via urine might be adequate to keep the concentrations of such NPs below the toxic threshold. More problematic would be highly fat-soluble NPs (or indeed any highly fat-soluble degradation products made by the organism in an attempt to degrade any ingested NP). Rather than being diluted throughout the body, fat-soluble NPs might accumulate in membranes or fat storage bodies and they could accumulate over long periods, eventually exceeding a toxic threshold. It is not unreasonable to look for an evolutionary solution to this problem that is generic rather than specific to each fat-soluble NP. Consequently, it is not surprising that there are some enzymes (e.g., cytochrome P450s) in the mammalian liver that act on molecules to add polar groups, such as hydroxy groups generating products that are more water soluble than the original NP. These enzymes typically have a broad substrate tolerance and so will act on many ingested compounds and will convert water-insoluble NPs to more water-soluble degradation products that will be diluted throughout the body and also excreted via urine. Thus, it is proposed that organisms will not have evolved ‘to degrade toxins’, rather they will have evolved to keep the concentration of exogenous chemicals below a toxic threshold. The very versatility of this system explains why most synthetic chemicals cause most organisms little harm—they have
evolved mechanisms to cope with NPs and they are usually good enough.

This combined strategy of degradation and excretion would work by ensuring that there is a flow of chemicals from the body, thus keeping the concentration of any chemical at any potential active site low enough to reduce the chance of a significant interaction occurring. Such mechanisms would not be perfect but they would usually be sufficient, they would be versatile and robust if combined with other mechanisms such as learned behaviour. Individuals that persistently ingested high levels of NPs that overwhelm the mechanisms would be selected from the population and the individuals that favour a different diet would thrive. Human societies have culture as well as individual behaviour to guide individuals towards diets that are tolerated.

**Isolation**

All organisms can be regarded as possessing several ‘compartments’. A cell is not a uniform entity rather it possesses a number of regions with specialised biochemical properties. These regions in eukaryotic cells can be surrounded by a membrane, thus they can possess some capacity to control their own environments. Once an organism is multicellular, the capacity for even greater spatial separation of functions becomes possible. The evolution of organs takes this specialisation a stage further. The ability of organisms to sequester (lock away) NPs in some limited regions of the organism might be another mechanism to avoid NPs accumulating in other more sensitive regions.
Adapting to a chemical

The past 100 years have shown us that organisms adapt to selective pressures imposed by the prolonged use of pesticides or drugs—organisms can adapt rapidly to new chemical selection agents. It is likely that such adaptation mimics the adaptation to NPs that has occurred in organisms throughout evolutionary time. An early example of organisms evolving the capacity to survive in the presence of a toxic chemical came shortly after the citrus growers in California had adopted the practice of exposing whole trees to hydrogen cyanide gas (by temporarily enclosing each tree in a portable ‘tent’) in order to kill insects overwintering on the tree. Within a few years of this practice being adopted around the beginning of the twentieth century, hydrogen cyanide no longer gave effective control of the insects, despite the fact that this gas is a very potent inhibitor of respiration. This surprising appearance of resistant organisms in response to intense selective pressure was to be the first of many examples that were reported during the twentieth century (Figure 6.4). Resistance of organisms to insecticides, fungicides, herbicides, some antimalarial drugs and antibiotics is now well known and a very serious problem. In insects exposed to unrelenting selective pressure, after 7–14 generations, it is usually possible to find mutants in a population that have developed some resistant to the normal dose being employed to control that organism. If the selection pressure is maintained, the descendants of the few surviving individuals will thrive and continued use of the insecticide at a higher dose will simply select for even higher resistance.

Now that the problem of resistance development is known, some strategies can be adopted which might reduce the rate of increase of resistance. For example, in some circumstances it is the exposure of some members of the population to sublethal doses for prolonged periods that increases the rate of development of resistance. Consequently, ensuring that the control agent is applied at the optimal concentration and for only a limited period can slow the rate of resistance development. Likewise, the use in sequence of two or more control agents, which operate by different mechanisms, can impose different selective forces in sequence and this normally reduces the rate of resistance development to either control agent. Furthermore, studies of antibiotic resistance in microbes suggest that although possessing the genes for
resistance might itself impose additional costs on the resistant organism, subsequent mutations can reduce these extra costs so the resistance gene can persist in a population even after the use of the selective agent has been stopped. The management of the development of resistance is one of the biggest problems facing the agrochemical and pharmaceutical companies because if such resistance appears during the patent life of the control agent, profits might be very seriously reduced or even eliminated.\(^{15}\)

Using the knowledge of the development of resistance to synthetic chemicals, one can predict that an organism encountering a new inhibitory NP in its food source, or in its environment, will evolve a capacity to adapt to the new chemical. By behavioural choices, or by chance circumstances, some individuals in the population will not be exposed to a lethal dose of the NP and the descendants of those individuals will eventually form resistant populations.

**Exploiting a chemical**

This topic is covered more fully in Chapter 8, where examples are given of NPs in the diet that are exploited rather than being degraded or excreted. (p.145)

The breakdown of NPs and synthetic chemicals—why chemicals do not accumulate in the environment

The existence of NPs has primed the world for synthetic chemicals and mechanisms evolved in response to NP loads on organisms are

![Figure 6.4. The evolution of resistance to toxin substances, as illustrated by insecticide resistance. As each new group of insecticide was widely adopted, resistance grew, but by the 1980s better management of pesticide use (e.g., Integrated Pest Management) helped to reduce the incidence of resistance for the newest insecticides (e.g., pyrethroids).](image)
being used by all organisms, including humans, to cope well with most synthetic molecules. This fact must not allow a complacency to develop about chemical pollution because, clearly, there are limits to the capacity of organisms to cope with chemicals in their environment, especially if those chemicals have some unusual properties (e.g., DDT). The analytical methods available to identify and quantify chemicals have advanced to the extent that few synthetic chemicals can hide from the determined investigator. However, analytical methods are always highly selective—they only find the substances sought or the chemicals with very similar properties to the one sought. Modern analytical methods have been used to follow the fate of only a very few of the chemicals made by humans and which are released into the environment. Although we have a very incomplete record of the fate of the great majority of synthetic chemicals, there is little evidence that many such chemicals are building up in the environment. Why? Once again an answer to that question requires us to consider the fate of the older, more numerous, more chemically complex chemicals that have been released into the world for millions of years—the NPs. There appears to be some steady state of NPs in the environment and the mechanisms that are maintaining that steady state must be understood. So, how are the hundreds of millions of tonnes of NP lost from the world every year?

**NP degradation—the NP cycle**

If 1% of the carbon fixed by photosynthesis is converted into NPs each year, without degradation processes returning this carbon back into the carbon cycle, within a century the total world's carbon would be tied up in NPs. Although there is some accumulation of fixed carbon in the soil (and in oil and coal deposits), there is very little evidence for a significant accumulation of any particular NPs in any ecosystem. One must conclude that there is some balance between the production and of the degradation of NPs. Given that many NPs are not extensively metabolised by the organisms that make them, other organisms must carry out a significant amount of this degradation. There must be pathways that lead from any NP back to carbon dioxide. **There must be NP cycles.**
Microbes—an essential part of the NP cycle

The organisms that have most impressed humans by their ability to degrade synthetic chemicals are microbes (in the old terminology bacteria and fungi). Whenever attempts have been made to trace the degradation of synthetic chemicals in soils, microbes are found to be the main contributors to metabolic degradation. It is thus reasonable to postulate that these microbes are also the main contributors to NP degradation although much less attention has been paid to the microbial degradation of NPs.¹⁷

Why do microbes degrade synthetic molecules?
The existing paradigm

By considering the microbial degradation of both synthetic and natural chemicals as one, some interesting questions arise. Why do microbes carry out degradative processes? The conventional view, which is nearly universally accepted, is that microbes have a capacity to adapt to the availability of any chemical and that some mutants in a population will gain fitness by using specific chemicals as a source of elements or energy. The mutant that can use a novel chemical as a source of carbon, nitrogen or phosphorus to sustain its growth will be fitter than other individuals in the competing population. This view is part of the more general concept of an ecological niche, where every species has evolved to gain resources in a particular manner, balancing the ease of access to the resource with the ability to compete with other organisms. Becoming a specialist reduces the number and maybe the amount of available resources but also reduces the number of competitors for that resource. There is considerable evidence to support this model as applied to microbial communities, some of them are impressive. The most convincing experimental findings come from experiments where microbes are isolated and grown on simple mixtures of pure chemicals. Typically, a mixture of simple salts provide nitrogen, phosphorus, (p.147) calcium and other minor elements and a single synthetic chemical provides the only carbon source for microbial growth. If any microbe can grow on this simple, well-defined culture medium, it must be able to access the carbon in the synthetic chemical; hence, the microbe must be able to break that chemical down into metabolisable substrates. The most well-known, simplest experimental method uses the algal polysaccharide agar to solidify the experimental solution on the base of a sterile Petri dish. A
A sterilised wire loop is used to smear a microbial sample (derived from a soil or water sample or from whatever source chosen for study) over the surface of the agar plate. After incubating the Petri dish for a period of days, it is usual to find just a few colonies of microbe growing on the provided mixture (Figure 6.5). From the millions of microbial cells on the agar plate, only a very few have an appropriate genetic makeup which enables them to degrade and utilise the synthetic chemical for growth. This is the nearly universal finding, irrespective of the nature of the synthetic chemical incorporated into the agar or the source of the microbial cultures. The proportion of individual microbes that can access the substrate varies considerably, and the species that grow will vary but it is a rare chemical that will not be degraded by some microbe. What is really remarkable is that such simple methodologies readily find, in most soil samples, microbes that can utilise any one of the large number of synthetic chemicals. Sometimes, one can increase the success rate of finding an appropriate microbe to grow on a specific chemical by choosing a soil sample known to have been previously exposed to the chemical being studied. However, often a microbe that can degrade compound X can be found in a soil that has never been exposed to X. Why should natural microbial populations contain microbes that can utilise apparently unnatural substrates?

(p.148) The traditional view is that there are such a broad range of natural chemicals in the environment, chemicals which bear some structural similarity to synthetic chemicals, that there will always be some microbe that has evolved to

Figure 6.5. Selective isolation of microbes capable of living on a novel chemical.
specialise in degrading such carbon sources. The microbe that specialises in accessing a strange chemical, a substance that is not accessible to less specialised organisms, will have an enhanced fitness because it has exclusive access to that resource. If one considers each specific molecular structure as being equivalent to a niche, it is predicted that specialised microbes will evolve to exploit that niche. When a soil sample is cultured with only a single synthetic molecule as the carbon source, the only microbes that will grow will be those capable of accessing similar molecules in the soil.

The extensive experience of growing microbes on synthetic chemicals has been exploited in attempts to reduce the chemical contamination of soils. If microbes can be grown on a synthetic chemical and if it is possible to multiply them in the laboratory, one should then be able to apply such cultures to the soil to enhance the natural populations in contaminated soils. However, this approach has had less success than might have been predicted. Why?
Criticisms of the model

The paradigm very simply outlined earlier is an attractive one but one with some worrying features. One of the difficulties is that the selective conditions that apply on a Petri dish in a laboratory are very different from those that pertain in the natural environment. The selection pressure that operates when a microbial population is given access to only one novel substrate, a substrate that occurs at high concentration in the agar with all other elements conveniently at hand, is very extreme indeed. The scenario is hardly a model of the real world. In most soils, there are a very wide range of carbon substrates available, the most common being cell wall polysaccharides (such as cellulose) from plant material. If rare unusual substrates do occur in the soil, which they undoubtedly do (e.g., NPs from the roots, fungal NPs or microbial NPs or NPs from the decaying leaf litter introduced into the soil by worms or simply washed into the soil by rains), each one will occur at a concentration well below the concentration of the more common carbon substrates. Under these circumstances, organisms accessing the most accessible carbon substrates will be most able to compete for nitrogen, phosphorus and other elements. The organisms that can readily grow on the most widely available and accessible substrates would be expected to outcompete slower growing microbes struggling to access some poor quality carbon source that was only present at very low concentrations. Consequently, it is quite hard to explain why individual microbes with an ability to use an unusual, intractable substrate that only occurs at low concentrations would survive in soils. The circumstances that allow it to blossom when grown under the freak conditions of a selective culturing on agar are just too bizarre to be relevant to its survival in the real world. Indeed, if a microbe that can survive on a unique substrate is isolated and then that microbe is placed on a more accessible substrate, the ability to thrive on the intractable substrate is quickly lost from the population. It has been shown (p.149) many times that if a microbe with an ability to degrade chemical X has been selected, if the microbe is grown on a more common carbon source such as glucose, mutants better suited to growing on glucose alone soon outcompete those able to use glucose and X. These findings explain why it is hard to use laboratory selected microbes to enrich the soil microflora in order to help breakdown some soil contaminant. Ignoring competition from existing soil microbes well adapted
to that soil, mutants of the newly added microbe that gained the ability to grow on more accessible substrates that occur in the soil would soon appear and these would compete the strains originally selected.

So why do microbes possess enzymes capable of degrading synthetic chemicals

The alternative model

As noted earlier in this chapter, organisms making NPs have been releasing huge quantities of complex molecules into the environment for billions of years. Consequently, it is reasonable to deduce that the presence of NPs in the environment has been a factor in the selection of microbes with exotic chemical degrading capacities. However, in Chapter 5, it was explained that organisms making NPs might possess a repertoire of enzymes with low substrate specificity; consequently, an existing mechanism to generate chemical diversity could also be of value when there was a need to metabolise chemicals. Could it be that the broad substrate tolerance of enzymes making NPs make them prime candidates to produce the new degradative capacity? In other words, could the versatile, flexible metabolism of NP synthesis be the resource most likely to be drawn on for NP degradation? Maybe the difference between making and degrading complex substances is a blurred one in microbes? In this scenario, synthetic chemicals introduced into the environment are simply bringing about a quantitative change but little novelty is needed by existing microbes to cope with these new molecules—as explained in Chapter 4, there are few fundamental differences between synthetic and naturally made chemicals.

What does this chapter tell us about the way science works?

It was only when I was unexpectedly asked to take over a third year module on ecotoxicology, when a colleague was ill, that I began to reflect on the way in which my knowledge of NPs might inform the new subject I was learning. Nowhere in my reading on pollution and toxicology did NPs appear but I did begin to realise that many books on pollution or ecotoxicology listed a rather small number of examples of chemicals that were a cause of concern. One book listed 80 chemicals in its index yet I had read elsewhere that tens of thousands of synthetic chemicals had been made industrially and I knew that estimates of the number of structures made naturally ran
into the hundreds of thousands. Being an avid reader of Arthur Conan Doyle, I recalled Holmes's deduction, given in the quote at the beginning of this chapter, that the lack of something happening was often highly significant. It is surely interesting and significant that tens of thousands of synthetic molecules seem not to have caused environmental concern and less than 100 are perceived as a problem. Instead of thinking about those 100, why not think about as to why the great majority were not a problem? Given that I had thought a lot about whether synthetic and natural chemicals differed, it suddenly occurred to me that there were no known problems caused by NP accumulation and that was also a significant fact. A consequence of putting these ideas together produced this, no doubt controversial chapter. However, what I think the chapter shows once again is that scientific subjects can become too closed and insular. The practitioners can become too comfortable within the parameters they (or their teachers) have set. All scientific knowledge needs to be joined together, yet so often we teach it as if each topic self-contained.

The way in which politics interacts with science is well illustrated by the EU Drinking Water Directive story. Politicians have been happy to follow scientific advice when it suits them and ignore it when such advice is politically inconvenient. One problem is that politicians, like many of the public, do not recognise that scientific advice is never going to be unambiguous because all scientists can do is to form an opinion about evidence, sometimes using a good theoretical understanding to make sense of the evidence but sometimes using a defective theoretical model to shape their thoughts. History should tell us that one generation’s orthodox scientific ideas have a habit of being overturned or greatly modified by the next generation. Our generation would be very arrogant indeed if they assumed that they are the first generation to have only the right ideas. Scientist must argue and disagree, that is their job. History tells us that the view held by the majority at any one time is not always correct; hence, the scientific advice to politicians can never be perfect, especially if it comes from one committee chaired by a single strong personality. Society would be better served if at least two independent committees could ponder any scientific issue of public concern and argue about their independent conclusions in an open, positive way. In other words, the model used to incorporate scientific knowledge into public policy badly needs
reform. Why otherwise would we still be doing so little about the potentially disastrous consequence of global warming yet still spending large sums to clean drinking water for no scientifically valid reason?

Notes:

(1.) In 1884, the Danish microbiologist Hans Christian Gram showed that the sequential treatment of bacteria, first with the purple dye **crystal violet**, then with iodine and at last a washing solution of alcohol, resulted in some species becoming pigmented. It was subsequently shown that the dye and iodine alone can diffuse into any cell but once inside the cell, the iodine interacts with the purple dye to form a chemical so large that it gets trapped in certain species of microbe, species which have a type of cell wall around the cell that makes it hard for large molecules to penetrate.

(2.) The word ‘screening’ means to use a method to isolate one item from many, on the basis of some property that the desired item might possess that the majority of items do not. The use of a **screen** or sieve to separate items on the basis of size was common in agriculture (seed cleaning), food production (flour) and manufacturing (sand, gravel, pigments, etc.). Biologists use the term to mean testing a large number of samples for one property.

(3.) Examples of selective toxicity were already known with the use of the poisonous metallic salts used to control fungi and weeds on crop plants. For example, Millardet, in 1895, had noticed that a mixture of copper sulphate and lime, applied to grapes alongside roads near Bordeaux to deter those on foot from stealing the ripe grapes, protected the grapes from mildew infection (the copper had an adverse effect on the mildew fungus without harming the vines). Soon ‘Bordeaux Mixture’ was being sold to farmers to protect potatoes from the fungus that causes blight (**Phytophora infestans**), a use which continues. The ability of sulphuric acid to kill some weeds in fields of grain, without harming the grain crop itself, is another example of differential uptake, where the waxy upright leaves of the wheat or barley shed the spray but the horizontal broad leaves of the weeds retain it.
(4.) Some have since argued that most of the wildlife changes detected in the 1950s, were mainly a consequence of the increasing adoption of the intensive, highly mechanised agriculture that characterised the post-Second World War food production. In northern Europe, for example, the centuries old patterns of agriculture changed due to mechanisation and the introduction of new crops, especially winter sown cereals to replace spring sown crops.

(5.) It is now known that there are many ways, other than direct toxicity, in which the use of a pesticide can adversely affect the population of a non-target organism. Suppose an insecticide is sprayed on a field to control a particular insect pest. The chances of any adult bird being directly sprayed are very low. More vulnerable are chicks, especially if they are fed insects that are dying from the insecticide exposure. However, maybe the biggest problem will be the starvation of the insect-eating chicks, if the insecticide works well. Likewise, a herbicide that is not directly toxic to birds can remove the food source (weed seeds) from a bird population.

(6.) Not all of the evidence was sound because the early analytical methods for DDT using gas chromatography could confuse PCBs (polychlorinated biphenols) and DDT breakdown products. However, these analyses alerted scientist and the public to the widespread contamination of the environment with PCBs (widely used in electrical transformers and other industrial equipments at that time but subsequently banned), which became a new concern.

(8.) Controversially, the politicians had responded to lobbying by the agrochemical companies not to make the new, more extensive safety testing retrospective immediately. Clearly, the removal of all products from the market for a new prolonged period of reassessment would harm the agricultural economy. Furthermore, it was argued that many products had been in widespread use for decades, with no evidence of harm, so such products had effectively been safety tested in the real world. However, this compromise did allow some rather doubtful chemicals to remain in use before being slowly phased out without ever being fully reassessed.

(9.) Many animal husbandry problems are caused by infectious agents. Fungal diseases, such as foot rot in sheep, were treated by chemicals (copper sulphate) that had also found a
use in controlling potato blight. Insects causing damage to hides in cattle or infestation of sheep were controlled by insecticides related to insecticides in crop use—as is the treatment of head lice in humans. The treatment of helminths (worms) in pigs is not dissimilar to the treatment of worms in humans. There are really no conceptual barriers to the exploitation of selective toxicity in any area of biology. Hence, the view that the agrochemical and pharmaceutical industries can be distinguished in terms of the scientific principles is wrong and unhelpful.

(10.) The inability of the public and of politicians to make rational judgements of risk is well documented. The key elements of an individual, in judging a risk are the degree of control the person has over the hazard, the dread of the outcome and the drama that might ensue from an accident. Thus, driving a car that carries a very much greater risk than eating food-containing additives and pesticide residues is judged safer by most consumers. This is because the driver is in control of the car but has no control of what is in their food. The car driver also tends to think of physical injury as the most likely outcome of a car accident whereas they often associate chemicals with the more dreadful cancer.

(11.) The EU Drinking Water Directive suffered from another real problem—there are multiple sources of pesticides in an individual's diet; hence, the elimination of pesticides from drinking water is hardly likely to help much if the food one consumes contains much more significant doses of the same pesticides that were expensively reduced in the water. The old toxicology rules ignored by politicians for drinking water are still applied to foods and allow consumers to eat significant amounts of many pesticides!

(12.) That number is so big that it means little to most people. Try thinking of the total mass of all humans, cows, pigs and sheep added together and you are getting there. It is possible that this is an underestimate because it is based on plant productivity and as plant material is degraded by microbes more NPs can be made.

(13.) Many human populations have only encountered some mixtures of NPs relatively recently—the first Europeans to encounter chilli peppers, many beans, pineapples, bananas, tobacco and so forth did so only a few hundred years ago. The
solanine alkaloids (and other NPs) in potato or tomato were unknown to Asians, Africans and Europeans until very recently, yet these populations seemed untroubled by these novel chemicals. Tomato fruits were initially considered to be poisonous when introduced to Europe and it was only in the nineteenth century that they became widely adopted as a food plant.

(14.) Organisms that have a very restricted diet can be expected to have evolved more specific mechanisms to target chemicals in the diet that are especially toxic substances. Thus, an insect living on one plant might protect itself against one toxin by specific biochemical traits—see Chapter 9.

(15.) However, resistance development just after the patent life expires helps to keep cheap generics out of the market, leaving the newer, patented, more expensive products to find a market.

(16.) An analogy would be that a method of detecting people, which only found those with red hair, would give a very misleading impression of the population of London.

(17.) The concentration of attention on synthetic chemicals is partly due to the need to fulfil regulatory requirements to study the fate of pesticides and other major industrial chemicals and partly due to the fact that the presence of NPs in the soil or in water has not been generally regarded as of importance or significance. It is also important to recognise that some degradation of NPs will occur through chemical degradation such as photo-oxidation.

(18.) For most of the twentieth century, it was assumed that all microbial organisms could be grown in culture if only the appropriate growth medium was found. However, when estimates are made, using molecular biological techniques, of the total number of microbial species in soil or water samples, it has been estimated that typically only 10% of the species present have ever been cultured.
