# 8 Legislation and Regulation

## Key Points

- Fungicide companies operate within a strict and detailed legislative and regulatory framework covering the safety and efficacy of products and manufacturing processes. The laws and regulations differ around the world.
- Regulatory regimes are subject to political as well as scientific factors.
- Fungicide users also operate within a strict regulatory framework designed to protect the environment, the farmer and the general public and to produce food that is free from damaging residues of pesticides.
- Consumers generally do not appreciate the safety of current fungicides or their importance in maintaining food security.
- Conventional farming must coexist with the so-called 'Organic' movement, which bans the use of most modern systemic fungicides.

## Introduction

The legislative requirements of fungicide registration are primary concerns for fungicide companies. The combined cost of registration, environmental testing and toxicology can add up to US$170 million per launched product or more than two-thirds of the total cost. A great deal of thought and experimentation goes into predicting and testing the properties of lead compounds so as to minimize the time and effort spent on compounds that are destined to fail to secure registration. It would be bad enough to have to abandon a compound late in development after perhaps US$200 million has been spent on its development. But far worse would be if a compound was released and subsequently found to have some deleterious effect. The loss of reputation and the payment of compensation to damaged parties could threaten the very viability of the company.

The purpose of legislation is to allow benefits to be obtained while incurring the least possible risk to the manufacturer, user, consumer and the environment. For pesticides, this includes a spectrum of activities from the patenting of a candidate product derived from synthetic or natural sources to the examination of its potential short- and long-term effects on humans, animals, plants and the environment.

Traditionally, legislative procedures and regulations have differed between countries. The current goal of standardizing pesticide registration regulations across nations ('harmonization') is intended to improve the effectiveness of industry and government resources and lower the costs associated with risk assessment that are eventually financed by the consumer.

## Registration Requirements

The legal requirements that define the process of fungicide development and use also apply generally to pesticides.

Effective pesticides, and particularly fungicides, are difficult to discover and predictably are subject to many more rigorous toxicological and environmental tests than pharmaceuticals before they can be sold. By comparison with pharmaceuticals, the action of using a fungicide to control a crop disease is equivalent to the selective and safe treatment of headaches using aspirin dissolved in water and sprayed in low volume from an aircraft over a town in which some of the sufferers are either inside buildings, and therefore protected from the application, or have not yet arrived on the scene. Fungicides are not usually applied to single, captive plants in the same manner as a pharmaceutical is used on a single patient. Consequently, factors other than safety to an individual become important in determining their safety. An outline of the testing processes and the timescale is given in Fig. 8.1.

Prior to their sale in any country, new and effective products must be shown to be safe to:

- the operator who handles and applies the product;
- the consumer of the treated crop;
- the environment; and
- the crop.

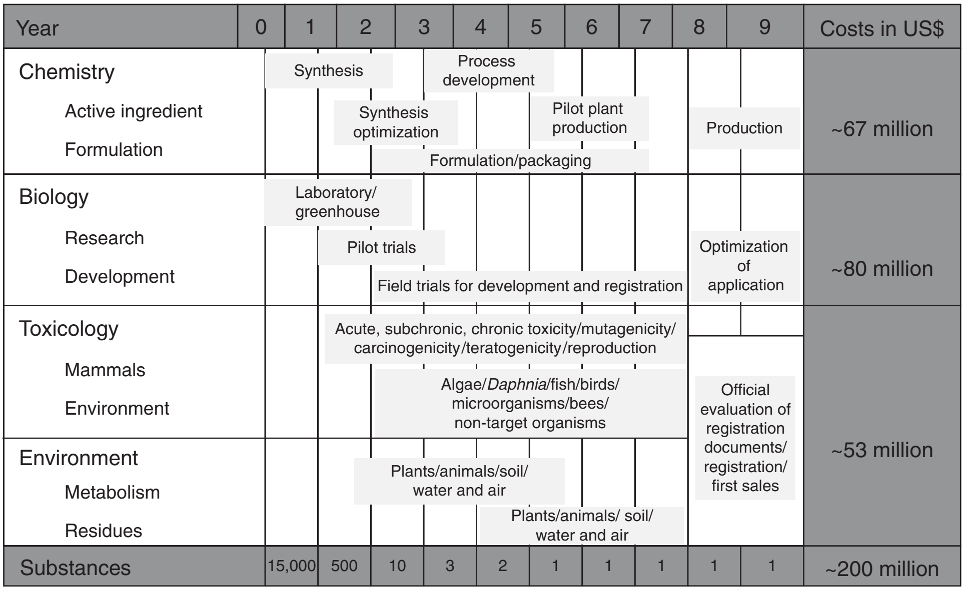

**Fig. 8.1.** Development of a crop protection product. (Courtesy of Andy Leadbeater, Syngenta, based on data from an ECPA study carried out by Phillips McDougall. © Phillips McDougall.)

In some countries, the product must be shown to be efficacious; that is, promote a significant yield increase. This requires the use of field trials for each crop and each pathogen in a representative range of agroecological zones.

More recently, regulations have been introduced that promote practices designed to prevent fungicide resistance and thus prolong the effective life of the compound. Initially, the acute toxicology of new compounds is determined so that advice may be given to researchers conducting chemical, biological and formulation studies and, if appropriate, to make decisions with respect to further development. As the candidate proceeds through the various stages of biological evaluation, the programme of studies widens to support the development of the compound and ultimately to satisfy the regulatory authorities.

The emphasis on global markets means that studies to define the safety of candidates must comply with the requirements of all the major regulatory authorities. Detailed guidelines are produced by individual countries and by international organizations such as the World Health Organization, the FAO and the Council of Europe.

## Toxicology

Toxicology studies are exercises in prediction. They are also extremely expensive and form the major component of the total development budget for a new fungicide. Consequently, tests are carried out only as they become necessary to progress a candidate towards registration.

A broad range of tests is employed, which examine the safety of new compounds in rats, mice, dogs and primates in a stepwise procedure, depending on the stage of development of the fungicide candidate. As this process is the most expensive of all development costs, the agrochemicals industry has good reason to welcome the development and acceptance of animal-free toxicology tests. However, the debate that questions the use of animals in toxicological tests has failed, so far, to produce an alternative that is acceptable to regulatory authorities.

Acute toxicology testing involves the derivation of the lowest dose resulting in 50% mortality ($LD_{50}$). $LD_{50}$ values are ranked according to toxicity. Values of less than 5 mg/kg body weight (bw) are very toxic; values between 5 and 50 mg/kg bw are toxic; those between 50 and 500 mg/kg bw are harmful. The $LD_{50}$ values for fungicides are generally high, demonstrating very low oral toxicities (Table 8.1).

$LD_{50}$ values are used to design subacute studies for longer-term evaluations of toxicology. These include 90-day feeding studies and others of up to 2 years' duration which explore possible chronic, oncogenetic (tumour-inducing), mutagenic and reproductive effects. The metabolic fate of the new fungicide in animals is also examined. Tests are planned strategically to coincide with nodal decision points corresponding to the maturity of other tests in the development programme (Fig. 8.1). It is current policy to review the toxicology of pesticides every 10 years.

## Environment

Fungicide use is intimately involved in ecosystem dynamics and new compounds are assessed for their potential impact in a variety of environments.

**Table 8.1.** Acute toxicology of a range of fungicides.

| Compound | $LD_{50}$ (rats) (mg/kg bw) |
|---|---|
| Benomyl | 10,000 |
| Captan | 9,000 |
| Chlorothalonil | 10,000 |
| Cyproconazole | 1,020 |
| Cyprodanil | 2,000 |
| Fenpiclonil | 5,000 |
| Fenpropimorph | 3,000 |
| Fentin | 140–298 |
| Iprodione | 3,500 |
| Kresoxim-methyl | 5,000 |
| Mancozeb | 5,000 |
| Metalaxyl | 669 |
| Polyoxin | 21,000 |
| Propiconazole | 1,517 |

$LD_{50}$, lowest dose resulting in 50% mortality; bw, body weight.

Most fungicides are applied as foliar sprays. Some are used as seed treatments. Logically, a significant proportion of the fungicide used to control disease finds its way into the soil where it may be degraded by microbial action or through direct chemical reaction, or move in the soil water and in direct runoff to water courses or to the underlying water table. Fungicides entering water courses may adversely affect aquatic life or the wildlife associated with a water environment. Likewise, fungicides may affect soil microorganisms or may be consumed by animals and introduced into food webs. It is necessary, therefore, that all new compounds at an appropriate stage of development are investigated with respect to their environmental fate and safety.

The first tests are straightforward, determining water solubility, lipophilicity, adsorption/desorption characteristics and hydrolytic capacity. With prior knowledge of the parameters that govern mobility of compounds in soil, reasonable predictions can be made of the potential environmental impact of the new compound. Subsequent tests probe the breakdown and metabolism of the candidate fungicide and its metabolites in soil and water.

The potential of a compound to leach is extremely important, and there is legitimate public concern about the presence of pesticides in drinking water. Leaching studies carried out in the laboratory may overestimate the potential of a fungicide to move in soil water but are useful in comparative tests with compounds of proven mobility. The use of lysimeters is now standard practice and can provide realistic measurements of fungicide movement over extended periods in a variety of soil types. In 1980, a European directive set the acceptable limit for individual pesticides in water at 0.1 ppb, although there is no toxicological basis for that level. Proof that fungicides are present at levels below 0.1 ppb often stretches the limits of the available analytical methods.

Lysimeter methodology, combined with the use of radio-labelled compounds, can also be used to investigate the fate of the parent and its degradation products in soils, in the presence and absence of crops. The effects of light, temperature, rainfall, moisture content, pesticide concentration and soil type in aerobic and anaerobic conditions may be determined over time and used to establish the half-life, and hence the time to 90% disappearance, of the fungicide.

Because of the possibility of runoff into water courses and, in the case of rice fungicides, the use of products in paddy environments, the toxicology of new compounds to aquatic fauna and flora is determined using fish (trout and carp), *Daphnia* and algae.

Tests on birds are routine and include both acute and chronic studies designed to mimic the effects of scavenging activity in seedling crops and at harvest. Other studies include those on beneficial insects, for example bees, earthworms and soil microorganisms. The effects of candidate fungicides are also assessed on non-target plant species (Table 8.2; Pilling *et al.*, 1996).

Predictions of the field performance of candidate compounds in the environment are based on the accumulated data, either directly or by the use of one of the many available mathematical models, for example the leaching estimation and chemistry model (Hutson, 1992). However, ultimately it may be necessary to confirm the results of laboratory and lysimetry experiments in field trials.

**Table 8.2.** Higher plants tested for azoxystrobin safety. (From Pilling *et al.*, 1996.)

| Family | Species |
|---|---|
| Dicotyledons | |
| *Amaranthaceae* | *Amaranthus retroflexus* (pigweed) |
| *Chenpodiaceae* | *Beta vulgaris* (sugar beet) |
| | *Chenopodium album* (fathen) |
| *Compositae* | *Bidens pilosa* |
| | *Xanthium strumarium* (cocklebur) |
| *Convolvulaceae* | *Ipomoea lacumosa* (morning glory) |
| *Cruciferae* | *Brassica napus* (oilseed rape) |
| *Euphorbiaceae* | *Euphorbia heterophylla* (spurge) |
| *Leguminaceae* | *Glycine max* (soybean) |
| *Malvaceae* | *Abutilon theophrasti* (velvetleaf) |
| | *Gossypium hirsutum* (cotton) |
| *Polygonaceae* | *Polygonum aviculare* (knotgrass) |
| *Rubiaceae* | *Galium aparine* (cleavers) |
| Monocotyledons | |
| *Cyperaceae* | *Cyperus esculentus* (yellow nutsedge) |
| | *Cyperus rotundus* (purple nutsedge) |
| *Gramineae* | *Alopecurus myosuroides* (blackgrass) |
| | *Avena fatua* (wild oat) |
| | *Digitaria sanguinalis* (crabgrass) |
| | *Echinochloa crus-galli* (barnyardgrass) |
| | *Oryza sativa* (rice) |
| | *Setaria viridis* (green foxtail) |
| | *Sorghum halepense* (johnson grass) |
| | *Triticum aestivum* (wheat) |
| | *Zea mays* (maize) |

An example of the process is seen in studies using quinoxyfen which showed the parent compound to be resistant to leaching and to be stable. Metabolic products were identified in a variety of different soil types and other environmental situations. The principal compounds were 5,7-dichloro-4-(4-fluorophenoxy)-3-hydroxyquinoline (3-OH-DE-795) in soil and water/sediment tests and 2-chloro-10-fluoro(1) benzopyrano(2,3,4-de)quinoline (CFBPQ) in water and air. A minor metabolite, 5,7-dichloro-4-hydroxyquinoline (DCHQ), which formed only under acid conditions (pH 4.2) in soil and water/sediment, was judged as irrelevant to the study (Fig. 8.2; Reeves *et al.*, 1996).

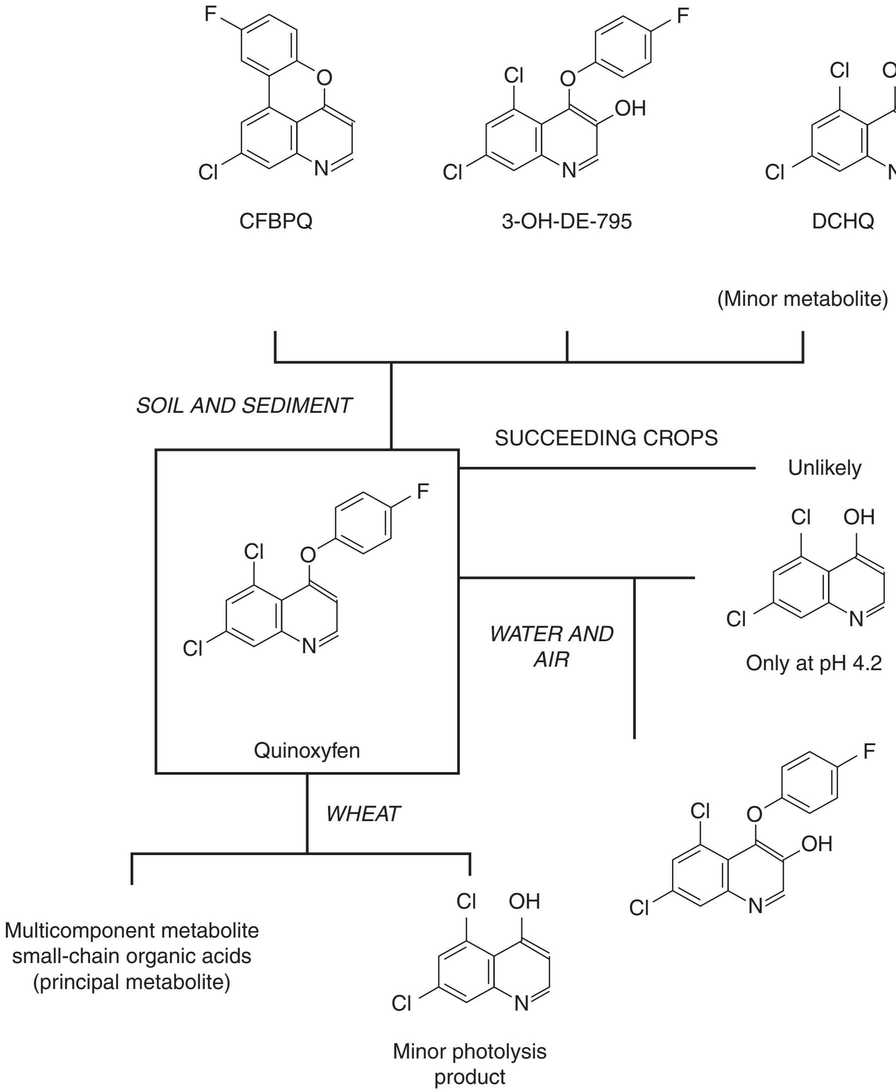

**Fig. 8.2.** Metabolites of quinoxyfen (CFBPQ, 2-chloro-10-fluoro(1)benzopyrano(2,3,4-de) quinoline; 3-OH-DE-795, 5,7-dichloro-4-(4-fluorophenoxy)-3-hydroxyquinoline; DCHQ, 5,7-dichloro-4-hydroxyquinoline). (From Reeves *et al.*, 1996.)

## Residues

The main point of exposure of the general public to any crop pesticide is at the time of consumption of the treated crop. For that reason, the quantity and quality of pesticide residues in the crop at harvest are determined. Additional studies on the fate of residues in cooking, baking, refining and processing, including taint testing, may be carried out.

Residue trials are conducted in field crops in a variety of environments over at least two seasons. As with crop phytotoxicity studies, residue trials employ twice the maximum optimum rate of application of the test compound. Furthermore, the potential for accumulation in meat and milk is determined. Any major metabolites of the parent compound that are discovered undergo an independent series of toxicology and environmental tests.

For example, the principal residues in wheat treated with quinoxyfen are predominantly the parent compound and a mixture of small-chain organic acids. Photodegradation of the parent on leaf surfaces produces a third and minor metabolite, DCHQ, which is present at much less than 0.4 mg/kg plant material. Studies on subsequent crops showed that quinoxyfen is unlikely to be taken up via the roots. It was also demonstrated that quinoxyfen was the only significant residue in edible plant tissue (Reeves *et al.*, 1996).

Several immunodiagnostic assays are available for the detection of certain fungicides in food, food products and the environment. The permitted levels for most fungicides are of the order of 1–20 ppm. Diagnostic assays, based on ELISA technology, have detection capabilities to 1 ppb. Benomyl, because of its widespread use and public safety issues, has attracted the most immunodiagnostic work (Charlton *et al.*, 1991). However, systems are developed for metalaxyl (Newsome, 1985), triazoles (Newsome, 1986; Forlani *et al.*, 1992), procymidone (Ferguson *et al.*, 1993), iprodione (Newsome, 1987) and fenpropimorph (Jung *et al.*, 1989). More recently, mass spectrometry methods have come to the fore.

Residue levels are dependent on the particular agricultural systems that apply in each country. Sunlight, rainfall and temperature conditions, soil types and crop storage methods differ between each country. Hence many countries require residue testing to be carried out under local conditions.

In 1992, a UK survey carried out by the Ministry of Agriculture, Fisheries and Food established that out of 3500 samples of various foodstuffs, less than 2% contained more than the maximum residue levels of pesticide, none of which was a fungicide.

## Operator safety

Operator safety is assessed in a series of experimental exposure studies carried out under practical conditions of fungicide application. In the UK, the Control of Pesticides Regulations (1986) require that persons handling pesticides, engaged in their distribution or applying them to crops are suitably qualified by validated examination.

Under the EU harmonization legislation guidelines for the setting and application, an operator exposure level (AOEL) has been established (http://ec.europa.eu/food/plant/protection/resources/7531_rev_10.pdf).

### Long-term risks

The highest concentration of the candidate fungicide that over the normal lifespan of test animals causes no observable effects (NOEL) is used to derive a value for an acceptable daily intake (ADI) for a person. Using residue data and a knowledge of the daily intake of various food crops, the ADI and the toxicological characteristics of the fungicide can be compared. Only if the ADI differs from the NOEL by at least a factor of 100 is the candidate considered to present no long-term risk to consumers of treated crops (Table 8.3).

In most cases, the consumption of synthetic pesticides in food is less than 10% of the ADI, even assuming an excessive intake of treated crops.

### Resistance risk

It is a requirement for registration of new fungicides under European Community legislation that an assessment of resistance risk, including details of a monitoring programme and baseline response data, and, if appropriate, a resistance management strategy should be supplied (Anon., 1991; Anon., 1993; Furk and Slawson, 1994).

### European Union regulation

The European Union (EU) has taken a vigorous stance on pesticide risks. It has promoted implementation of Council Directive 91/414/EEC (see http://ec.europa.eu/food/plant/protection/index_en.htm) and its successors.

Moves to unify national registration requirements are designed to allow the entry of pesticides to all EU countries operating under the legislation (Lynch and Feeley, 1992). The directive enforces a review of all existing products and, recognizing

**Table 8.3.** Acceptable daily intake (ADI) and no observable effect level (NOELs) for a range of fungicides.

| Compound | ADI (mg/kg bw) | NOEL (rats) (mg/kg diet) | NOEL (dogs) (mg/kg diet) |
|---|---|---|---|
| Benomyl | 0.0200 | 2500 | 500 |
| Captan | 0.1000 | 2000 | – |
| Chlorothalonil | 0.0030 | 60 | 120 |
| Fentin | 0.0005 | 2 | 5 |
| Iprodione | 0.3000 | 1000 | 2400 |
| Mancozeb | 0.0500 | – | – |
| Metalaxyl | 0.0300 | – | 250 |
| Triadimenol | 0.0500 | 125 | – |
| Flusilazole | 0.0010 | 10 | 5 |
| Vinclozolin | 0.0700 | 27.1 | – |

bw, body weight.

the need for a balance between the essential role of pesticides in food production and the social and political constraints, will work towards:

- removal of confidentiality of testing;
- minimal use of vertebrates in testing;
- ensuring that no unnecessary pain or suffering is caused;
- maintenance of the precedence of safety and the environment over the need to produce crop protection agents;
- ensuring that candidate pesticides can provide real benefit; and
- promotion of the principles of integrated management.

Implementation of the European directive and of comparable schemes in the USA (Jellinek and Gray, 1992) has been subject to considerable delay and debate, which has affected the progress of new materials through to registration and has impeded the re-registration of older products.

In 1992, the Organization for Economic Co-operation and Development initiated a pesticide programme with the aims of harmonizing pesticide assessment and control procedures, speeding the process of re-registration of established products and reducing risk. Comparative studies are in progress to evaluate differences between member countries. For example, iprodione is one of seven pesticides chosen as benchmarks in the assessment of data review procedures and involves the cooperation of authorities in the USA, UK, Canada, Australia and Finland, and the FAO (Grandy and Richards, 1994).

The European Parliament now espouses the need to eliminate compounds that pose a particular *hazard* to the public or the environment. Previously, the evaluation process attempted to quantify the *risk* of a deleterious effect. A compound is defined as hazardous if it generates a deleterious effect at any concentration. One of the most contentious hazards is so-called ‘endocrine disruption’. Endocrine disruption is manifested as, for example, alterations in sex organ development in molluscs (Bielza *et al.*, 2008; Gisi and Leadbeater, 2010). The fungicide industry argues that the concentration of compound that causes disruption should be compared with the concentration of the compound that is likely to be found in contaminated land, water courses or food products, but this proviso is not recognized by the authorities. Furthermore the agrochemical industry argues that elimination of the pesticide might lead to increased disease losses, lower food yields and higher food prices, which might be much more damaging to the health of the population than the fungicide. In response to this argument, the EU has introduced the notion of ‘substitution’. This device states that if a ‘hazardous’ compound could be substituted by a compound with the same or similar crop protection properties, then the hazardous compound can be withdrawn. The result of these regulations has been the wholesale withdrawal of compounds from the market. About 50% of the 400 relevant products have been withdrawn (Bielza *et al.*, 2008). Many of these compounds were old and out of patent. The decision to withdraw was taken in some cases not because of toxicity but because the cost of maintaining registration could not be covered by future predicted sales. Hence some useful products for small markets may have been inadvertently lost.

The Danish government has added an extra layer of regulations designed to reduce the use of pesticide in its country. Around 2000 it introduced a simple regulation limiting the total *mass* of pesticide that can be applied to the fields. This straightforward but blunt measure had the effect of promoting the use of compounds with high specific activity regardless of whether the compound was hazardous at the standard rate.

A more complex system has recently been introduced (L.N. Jorgensen, 2013, personal communication). Under this system, the fungicide is scored by the authorities for a range of toxic properties. The score is then used to set a tax for the pesticide. Hence a farmer needs to weigh up the extra cost of a fungicide versus the control that a particular compound affords. This system has placed a particular burden on the DMI group of fungicides that are coincidentally the mainstay of cereal disease protection. It is estimated that if DMI fungicides were withdrawn, food prices would rise by 20% and the EU would cease to be a wheat exporter.

### Resistance in medical fungi

A new and urgent threat to agricultural fungicide use has emerged from studies of fungicide resistance in medically important fungi (Arendrup *et al.*, 2010; Camps *et al.*, 2012; Chowdhary *et al.*, 2012). The main culprit is the fungus *Aspergillus fumigatus,* which is the cause of invasive aspergillosis (IA) in humans. This disease has increased in importance in recent years due to the prevalence of immune-compromised patients emerging from transplant surgery and HIV/AIDS treatment. DMIs have been used, and indeed were their original use, to control IA. The disease is hard to control and patients receive DMI treatment for weeks or months. Recently isolates of the pathogen recovered from affected patients were shown to display resistance to the triazoles. Genomic studies highlighted mutations in the *cyp51* gene.

IA is believed to result from the inhalation of *A. fumigatus*, which is a ubiquitous environmental fungus. The threat to the DMIs comes from the finding that environmental isolates of the fungus also have the mutations in the *cyp51* gene. The epidemiology of IA suggests that the fungus never sporulates in humans and so cannot transfer from human to human. Hence selection for DMI resistance in humans cannot be blamed. It is therefore suggested that the mutations in environmental samples have been selected by the use (or misuse) of agricultural fungicides. However, sources within the fungicide industry point out that DMI fungicides are also widely used in domestic situations more likely to be relevant for immune-compromised patients. These uses include paints, carpets and other textiles used both in the home and hospital. The resolution of this debate may decide the fate of DMI fungicides.

## Organic Farming

Organic farming is a broad term that includes a number of official and private schemes that are united by their rejection of synthetic fertilizers and modern pesticides, in particular fungicides. The movement grew rapidly in the 1980s and 1990s but seems to have peaked following the 2007 global financial crisis. In Europe, the number of farms adopting an organic farming regime increased from 7800 to over 55,000 between 1986 and 1996, with an area expansion from 0.12 to over 1.3 million ha (Lampkin, 1996). Similarly, in Germany and Austria organic farming developed from a proportional land use of about 0.5 to 4.6% overall (1.6 and 7.6%, respectively). Financial incentives are available to farmers in many European countries to convert to organic food production. In support of this policy, further provision has been made to carry out research and development programmes, together with educational and training initiatives.

However, contrary to the amount of publicity that accompanies organic farming, the sales of organically produced food have not been significant. In 1991, sales were estimated to be between 1 and 5% of the total production, with a forecasted growth to 10% by 1997 (Lunt, 1991). The reasons for the discrepancy are uncertain, given the strength of public opinion against the use of pesticides, but Lunt includes:

- conflicting interests in the retail trade between the maintenance of their conventional sales compared with the promotion of a niche market;
- high cost of food production, created by high labour and distribution costs and uncertain yields, that are subsequently supported by the consumer;
- the imposition of premium prices for organically grown produce may deter buyers;
- variability of supply and quality will impact upon shelf life for retailers and purchasers;
- the poor appearance of produce, particularly fruit, is of concern especially to those who buy from conventional sources, affecting the readiness of uncommitted buyers to purchase organic produce; and
- the authentication of food sources may be uncertain and the buyer has no clear understanding of what constitutes organically grown food.

Organic agriculture relies on the use of natural inputs and a self-styled sympathetic view of nature to support the claim that the food produced is more wholesome, of greater quality and generated in an environmentally friendly manner. Part of that philosophy relies on the conviction that ‘natural’ means healthy and, by implication, ‘man-made’ is unhealthy or corrupt. Several reports address this issue in detail (see Lunt, 1991) but, in terms of crop disease control and the value of fungicide use, the salient points are outlined here.

Several fungi produce mycotoxins which in their various forms can be carcinogenic, teratogenic (induce malformation of the fetus) and directly affect the nervous system. They are not uncommon and infect a range of crops including rice, legumes, onions, celery, marrow, peanuts and tomato (Moreau and Moss, 1979; Riemann and Bryan, 1979; Canning and Lansdown, 1983; Lunt, 1991). Aflatoxin, with a lethal dose of 0.25 mg, is 2000 times more toxic than the insecticide parathion and is produced in large quantities in diseased legumes, especially peanuts. Patulin, produced by *Penicillium expansum*, a common fruit-rotting fungus, induces acute and chronic disorders in animals and has been reported as a contaminant of fruit juice and drinks. The fungus C. *purpurea* causes ergot of graminaceous hosts. Ingestion of infected grain, particularly rye, which is especially susceptible to infection, results in internal haemorrhaging, abortion and death. The symptoms gave rise to the name St Anthony’s fire and the disease was commonplace throughout Europe during the Middle Ages. Fortunately, poisoning due to mycotoxins is rare because of quality control measures. The benefits of fungicide use in combating the infections that led to mycotoxin production cannot be ignored, however. Although fungicides are not used for the specific control of C. *purpurea*, it is interesting that the number of cases of St Anthony’s fire in Europe is increasing and it is tempting to speculate that the removal of fungicides from niche market cereal production, such as organic rye cultivation, may be encouraging this revival.

However, the argument that promotes the use of fungicides as a safeguard against the contamination of food by mycotoxins is not robust, as shown in studies on *Fusarium* diseases in cereals. Several mycotoxins are associated with *Fusarium* in cereals and they are known to be harmful to animals, including humans. Although the use of fungicides to remove the risk from mycotoxin poisoning is valid when infection is completely prevented, fungicide applications to established infections may affect the level of mycotoxin produced, depending upon the active ingredient and the toxin (D'Mello *et al.*, 1996).

Laboratory studies using *in vitro* cultures of *Fusarium* demonstrate the stimulation by fungicides of some mycotoxins concurrent with a decline in others (Table 8.4). Under field conditions the results of similar studies are conflicting, but the conclusion must be that the long-held view that fungicides are always beneficial by virtue of their preventive action against mycotoxin contamination in food is not well founded, and should be investigated further.

In addition to the toxins produced by the pathogenic fungi, plants also respond to invasion by releasing a powerful array of chemical defence mechanisms. In evolutionary terms, this is to be expected: because of their physical inability to escape attack, plants, unlike animals, have developed chemical means to evade damage. The majority of these compounds have not been studied but some, like the glycoalkaloids present in potatoes at levels up to 500 ppm, would prevent the sale of potatoes if the rules that govern fungicide and pesticide registration were applied.

Some natural toxins, for example nicotine, have been known for many years, and some have been incorporated into folklore. There is a certain contradiction in the argument that promotes 'natural' farming systems on the grounds of safety because it places no reliance upon synthetic toxicants to control pests, but then advises the use of highly toxic chemicals, albeit of natural origin. However, there are few fungicides of natural origin. Lime, copper and sulfur mixtures, including Bordeaux mixture, are commonly recommended as protectant materials. Copper-based products are effective fungicides and have a widespread use in crop protection in high-input farming systems as well as in organic agriculture, reflected in their global sales value. They are not without problems; copper poisoning can lead to neurological and kidney dysfunction. If used incorrectly, crops can be severely damaged, high levels of copper may accumulate in soils and their overuse in fruit crops may result in taint problems. In contrast, sulfur is less toxic but can be phytotoxic and can cause skin and eye irritation.

**Table 8.4.** *Fusarium* spp. mycotoxin production in response to fungicides.

| Fungicide | Pathogen | Effect on toxin production |
|---|---|---|
| Dicloran | *Fusarium graminearum* | DAS reduced or inhibited |
| Iprodione | (PDA broth culture) | ZEN reduced or inhibited |
| Vinclozolin | (PDA broth culture) | ZEN reduced or inhibited |
| Tridemorph | *Fusarium sporotrichioides* | T2 inhibited at 6 μg/ml<br>DAS inhibited at 6 μg/ml<br>T2 stimulated at 36 μg/ml |
| Carbendazim | *F. sporotrichioides* (PDA agar) | T2 increased at 5 μg/ml |
| Difenconazole | *Fusarium culmorum* (PDA agar) | 3-ADON increased at 0.1 μg/ml |

DAS, diacetoxyscirpenol; ZEN, zearalenone; T2, T2 toxin; 3-ADON, 3-acetyl deoxynivalenol.

Much of the publicity that surrounds the use of organic farming suggests that it is an advanced and enlightened method of crop production. In fact, most of the world uses methods of food production that are more like organic farming than high-input systems and, historically, organic farming was the only method of food production.

Organic farming is characterized by variable yields, occasional crop failure and, in extreme cases, famine. Only 150 years ago, European agriculture was suffering under the threat and, for some, the reality of crop failure. Crop disease epidemics, notably potato blight, went unchecked and the course of history was changed. Organic agriculture is not new and the potential problems associated with it are still present.

It is difficult not to draw a comparison between the historic and current geographic distribution of food-insecure people and the use of low-technology farming. In a recent report, it was stated that 'Organic methods simply cannot produce the quantities and qualities of food required by 20th century society' (Lunt, 1991). The same conclusion was reached in a recent symposium on the use of crop protection products and food quality (Anon., 1997). The growth of organic farming represents, and should remain, no more than a minor part of total crop production if we are to avoid the disasters that, in Europe at least, we appear to have forgotten.

## Consumer Values and the Agrochemicals Industry

It is difficult to quantify the effect of consumer pressure on the activities of the agrochemicals and fungicide manufacturing industry. However, a poll of boardroom managers in the chemicals industry identified a growing concern for environmental issues. Over 60% reported that, despite the current restrictions on resources, environmental matters have become a strong factor in investment strategy, with nearly half committed to significant spending to comply with environmental obligations. In the agrochemicals industry, the demands of registration authorities already account for much of the expense involved in pesticide discovery. The controls associated with the production of agrochemical products are much stronger and more established than in other sectors of the chemicals industry, arguably even more robust than in the pharmaceuticals industry. However, the increasing demands of legislative authorities and public pressure groups ensure that no one can afford to be complacent.

The changes in legislation are the main impetus behind the increasing boardroom awareness of the importance of environmental issues. While nearly 40% of managers acknowledge the influence of current and future legislative requirements, social responsibility was cited by only 25% of managers as a determining factor. Clearly, in the upper levels of management the consumer movement has yet to make a major contribution to discovery strategy.

## References

Anon. (1991) Council Directive (91/414/EEC) concerning the placing of plant protection products on the market. *Official Journal of the European Community* L230, 1–32.

Anon. (1993) Commission Directive (93/711EEC) amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. *Official Journal of the European Community* L221, 27–36.

Anon. (1997) *Crop Protection Agents and Food Quality: Meeting Customer Requirements, 17–19 September, 1997, University of Kent, Canterbury, UK*. BCPC/ANPP Monograph No. XX. British Crop Protection Council, Farnham, UK.

Arendrup, M.C., Mavridou, E., Mortensen, K.L., Snelders, E., Frimodt-Møller, N., *et al.* (2010) Development of azole resistance in *Aspergillus fumigatus* during azole therapy associated with change in virulence. *PLoS ONE* 5(4), e10080.

Bielza, P., Denholm, I., Loannidis, P., Sterk, G., Leadbeater, A., *et al.* (2008) The impact of a declining European pesticide portfolio on resistance management. *Outlooks on Pest Management* 19(6), 246–248.

Camps, S.M.T., Rijs, A.J.M.M., Klaassen, C.H.W., Meis, J.F., O'Gorman, C.M., *et al.* (2012) Molecular epidemiology of *Aspergillus fumigatus* isolates harboring the TR34/L98H azole resistance mechanism. *Journal of Clinical Microbiology* 50(8), 2674–2680.

Canning, D.M. and Lansdown, A.B.G. (1983) *Toxic Hazards in Food*. Croom Helm, London.

Charlton, R.R., Majaran, W.R., Carlson, C.W., Carski, T.H., Liberatore, E.A., *et al.* (1991) Environmental monitoring of crop protection chemicals by immunoassay. In: *Abstracts of the 105th AOAC Meeting, Phoenix*. Association of Official Analytical Chemists, Arlington, Virginia, no. 326.

Chowdhary, A., Kathuria, S., Xu, J., Sharma, C., Sundar, G., *et al.* (2012) Clonal expansion and emergence of environmental multiple-triazole-resistant *Aspergillus fumigatus* strains carrying the TR34/L98H mutations in the *cyp51A* gene in India. *PLoS ONE* 7(12), e52871.

D'Mello, J.P.F., Macdonald, A.M.C., Postel, D., Dijksma, W.T.P., Dujardin, A. and Placinta, C.M. (1998) Pesticide use and mycotoxin production in *Fusarium* and *Aspergillus* phytopathogens. *European Journal of Plant Pathology* 104(8),741–751.

Ferguson, B.S., Kelsey, D., Fan, T.S. and Bushway, R.J. (1993) Pesticide testing by immunoassay at trace levels in environmental and agricultural samples. *Science of the Total Environment* 132, 425–428.

Forlani, F., Arnoldi, A. and Pagani, S. (1992) Development of an enzyme-linked immunosorbent assay for triazole fungicides. *Journal of Agricultural and Food Chemistry* 40(2), 328–331.

Furk, C. and Slawson, D.D. (1994) Pesticide resistance and the EC plant protection products directives. In: Heaney, S., Slawson, D., Hollomon, D.W., Smith, M., Russell, P.E., *et al.* (eds) *Fungicide Resistance*. BCPC Monograph No. 60. British Crop Protection Council, Farnham, UK, pp. 385–388.

Gisi, U. and Leadbeater A. (2010) The challenge of chemical control as part of integrated pest management. *Journal of Plant Pathology* 92(Suppl. 4), S4.11–S14.15.

Grandy, N.J. and Richards, J. (1994) International harmonisation of pesticide control procedures – the DECO Pesticides Programme. In: *Proceedings of the Brighton Crop Protection Conference 1994 – Pests and Diseases*, Vol. 3. British Crop Protection Council, Farnham, UK, pp. 1409–1418.

Hutson, J.L (1992) The use of models in the regulatory process. In: *Proceedings of the Brighton Crop Protection Conference 1992 – Pests and Diseases*, Vol. 3. British Crop Protection Council, Farnham, UK, pp. 1253–1260.

Jellinek, S.D. and Gray, E.C. (1992) Some lessons from the United States reregistration programme. In: *Proceedings of the Brighton Crop Protection Conference 1992 – Pests and Diseases*, Vol. 3. British Crop Protection Council, Farnham, UK, pp. 1261–1266.

Jung, E., Meyer, H.H.D. and Hamm, R.T. (1989) Development of a sensitive ELISA for the fungicide, fenpropimorph. *Journal of Agricultural and Food Chemistry* 37(4), 1183–1187.

Lampkin, N. (1996) Organic farming – rapid European expansion. *Pesticide News* 33, 7.

Lisansky, S.G. (1994) International harmonization in biopesticide registration and legislation. In: *Proceedings of the Brighton Crop Protection Conference 1994 – Pests and Diseases*, Vol. 3. British Crop Protection Council, Farnham, UK, pp. 1397–1402.

Lunt, G.G. (1991) *Organic vs Conventional Crop Production*. GRO-ACT.

Lynch, M.R. and Feeley, D.F. (1992) The European Communities registration regime: the role of science, challenges and opportunities. In: *Proceedings of the Brighton Crop Protection Conference 1992 – Pests and Diseases*, Vol. 3. British Crop Protection Council, Farnham, UK, pp. 1243–1252.

Moreau, C. and Moss, M. (1979) *Moulds, Toxins and Foods*. Wiley, Chichester, UK.

Newsome, W.H. (1985) An ELISA for metalaxyl in foods. *Journal of Agricultural and Food Chemistry* 33(3), 528–530.

Newsome, W.H. (1986) Development of an enzyme-linked inununosorbant assay for triadimefon in foods. *Bulletin of Environmental Contamination and Technology* 36, 9–14.

Newsome, W.H. (1987) Determination of iprodione in foods by ELISA. In: Greenhalgh, R. and Roberts, T.R. (eds) *Pesticide Science and Biotechnology. Proceedings of the 6th International Congress of Pesticide Chemistry, Ottawa, Canada, 10–15 August 1986*. Blackwell Scientific, Oxford, pp. 349–352.

Pilling, E.D., Earl, M. and Joseph, R.S.I. (1996) Azoxystrobin: fate and effects in the terrestrial environment. In: *Proceedings of the Brighton Crop Protection Conference – Pests and Diseases*, Vol. 1. British Crop Protection Council, Farnham, UK, pp. 315–322.

Reeves, C.L., Gambie, A.R. and Baloch, R.I. (1996) DE-795: an environmental and exposure assessment. In: *Proceedings of the Brighton Crop Protection Conference 1996 – Pests and Diseases*, Vol. 3. British Crop Protection Council, Farnham, UK, pp. 1169–1174.

Riemann, H. and Bryan, F.L. (1979) *Food Borne Infections and Intoxications*. Academic Press, London.