Field research for the authorisation of pesticides

To the Minister of Health, Welfare and Sport

Subject	:	Submission of report on plant protection products
Your reference	:	GZB/C&O/971541
Our reference	:	U 1746/97/HvD/HB/446/2-IJ
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Dear Minister,

On 15 April 1997, you asked the Health Council to prepare a report dealing with the ways in which field research and laboratory or open-air research involving model ecosystems may be used to support environmental risk assessment for pesticide registration purposes. With this in view I have established a committee, which has examined this matter. Having also consulted the Standing Committee on Ecotoxicology, I am now able to present the Committee's report. As requested, I am forwarding copies of this report to the Minister of Housing, Spatial Planning and the Environment, the Minister of Transport, Public Works and Water Management, the State Secretary for Agriculture, Nature Management and Fisheries, and the State Secretary for Social Affairs and Employment.

The Committee believes that field research can be useful in connection with the registration of pesticides. This conclusion is, however, qualified by a number of critical observations. Tests conducted in the field or using model ecosystems by or on behalf of a manufacturer can be used to obtain evidence indicating that adverse effects which could not be excluded on the basis of modelling or toxicity testing in the laboratory do not actually occur in practice. However, to provide reliable evidence of this kind, a test must meet very stringent quality requirements.

Yours faithfully,
(signed)
Professor dr JJ Sixma

Field research for the authorisation of pesticides

To:

The Minister of Health, Welfare and Sport

The Minister of Housing, Spatial Planning and the Environment

The Minister of Transport, Public Works and Water Management

The State Secretary for Agriculture, Nature Management and Fisheries

The State Secretary for Social Affairs and Employment

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Executive summary

The Minister of Health, Welfare and Sport, also on behalf of other members of the government, has requested the Health Council to review the role that results from field research can play in ecotoxicological risk assessment for the authorisation of pesticides. In this advisory report a committee of the Health Council complies with this request. It interprets the term ‘field research’ in its broadest sense: the Committee understands field research to mean all of the research that exceeds the level of the standard ‘single-species’ toxicity test in the laboratory. This might include ‘multi-species’ toxicity tests in the laboratory, research on model ecosystems in the laboratory, glasshouse or in the open air and tests in ditches, field margins, agricultural fields etc. Within this category the Committee also includes tests aimed at studying the behaviour of a pesticide in intact soil profiles. What is common to investigations of this kind is the fact that they set out to achieve a closer approximation of the field situation. The Committee confines itself to the agricultural pesticides (plant protection products). These are used to protect agricultural crops or to keep uncultivated land free of weeds.

Legislation and authorisation procedure

The authorisation (registration) of pesticides in the Netherlands is regulated in the Pesticides Act. This stipulates that compounds may only be brought onto the market if, when used as directed, they are sufficiently effective and do not cause any unacceptable damage to the crop, to humans, to plants and animals (except target organisms), or to water and soil quality. A more detailed elaboration of the environmental requirements for

plant protection products can be found in the Pesticides Environmental Authorisation Requirements Decree. Dutch legislation has to a great extent been brought into line with the European Union directives in this area - the Authorisations Directive and the so-called 'Uniform Principles'.

The Board for the Authorisation of Pesticides (CTB) evaluates the acceptability of pesticides in the Netherlands on behalf of the government. This evaluation is performed with reference to a dossier which the applicant (usually the manufacturer or importer) must submit with his application for authorisation. This dossier contains data about the use of the substance, its physical and chemical properties and its toxicity for certain standard test organisms. In answering the question of whether a given compound satisfies the environmental requirements, the CTB follows a 'tiered approach'. The first tier comprises a broad, relatively stringent evaluation – based on model calculations – of the behaviour of the substance in the environment and of the submitted toxicity data. A substance which, according to that evaluation, satisfies the environmental requirements is considered to be acceptable - at least as far as environmental safety is concerned. Otherwise, the applicant is given the opportunity to submit additional research data. Based on this data, a renewed evaluation of environmental risks takes place (the second tier). If it appears likely from this data that the requirements are not exceeded under field conditions or that no unacceptable effects will occur, the substance is still authorised. In case of doubt, it is possible to issue a restricted authorisation, which is contingent upon research conducted under field conditions. Based on the resultant data, a definitive assessment is then carried out (the third tier). Every plant protection product that receives authorisation must be regularly reviewed. This usually takes place every five years.

Field research prior to authorisation

Field research is one of the ways in which an applicant can obtain the additional data for the second tier of the risk assessment. Because this is carried out prior to authorisation, the Committee speaks of pre-registration research. In an international context, guidelines have been established for the design and execution of various sorts of field research.

The Committee believes that this type of research can provide valuable additional data about the behaviour of plant protection products in the field, the exposure of non-target organisms and the resultant effects at population, community and ecosystem level. Experience gathered to date has shown, however, that it is frequently unclear how that data might be (or would need to be) used in reaching a decision about authorisation. The Committee discusses the causes and makes recommendations for improvements. It is of the opinion that it is not possible to reach a decision about the authorisation of a plant protection product until it has been clearly specified what is understood by an

'unacceptable effect'. Clarification of this point has both a policy-related and a scientific aspect. The former aspect concerns the government's protection objectives. In the Committee's opinion, these have not been sufficiently clearly formulated in the Pesticides Environmental Authorisation Requirements Decree and in the Uniform Principles. For example, it is unclear whether the government wishes to protect organisms at a species level or at a higher taxonomic level, or whether it primarily wishes to preserve functions (pollination, soil mixing, predation, etc.). The scientific aspect relates to the ecological significance of effects. The response of populations and communities of organisms in shallow, fresh water to exposure to plant protection products is relatively well known. This applies to a much lesser extent in relation to other populations and communities. It is therefore unclear what induced changes mean for the fulfilment of the protection objectives. For these populations and communities, it is, for the time being, still only possible to draw the line between acceptable and unacceptable effects with an ample safety margin. This, according to the Committee, is one of the main reasons for the problems that are encountered in interpreting the results of field trials for the purposes of decisions about authorisation. The Committee believes that criteria and preconditions need to be developed in order to identify what the acceptable (or unacceptable) ecological effects are.

Recoverability could, according to the Committee, play a role in decision-making about the authorisation of plant protection products. However, we need to specify precisely what it is that is recovering and ask ourselves whether the original changes have not, in turn, led to other, lasting developments. In the latter case, we need to ask ourselves what the ecological significance of such developments is and whether they are incompatible with the protection objectives.

The Committee recommends setting up field trials with a view to investigating possible effects of plant protection products on organisms according to a multi-concentration design, whereby systems that have been treated with different dosages of a compound are compared with untreated control systems. It regards a solid statistical input as an essential element in setting up such a trial and analysing the measurement results that are obtained. The Committee points out that designing field trials for the purpose of demonstrating the absence of previously (*i.e.* in the first tier) presumed effects, places great demands on the quality of the trial, especially with regard to its statistical power. This must be sufficient to allow for the detection of changes that might be regarded as ecologically relevant. Only then does the absence of a statistically significant effect mean that there has, in all probability, been no ecologically relevant effect. When presenting NOEC values, the Committee recommends recording the limits of the (95%) confidence interval for the true effect.

A field trial can only be used in assessing the acceptability of a plant protection product if it is possible to deduce from the results whether, under the broad range of

field conditions, no effects will emerge that might be regarded as unacceptable. This can best be guaranteed by conducting several tests under different conditions, but this appears not to be feasible in most cases for reasons of cost. In that case, the Committee considers a realistic worst case approach to be a good alternative.

Field research following authorisation

If, after the second tier in the risk assessment, there is still too much uncertainty about the safety of the plant protection product, it may be sensible to grant a substance a restricted authorisation on the condition that further field research is conducted into the environmental effects under field conditions. The results can be used for a third tier in the risk assessment procedure. Because investigators will then usually have a clearly defined research question, which has been dictated by all previous research results, and because this research takes place after (restricted) authorisation, the Committee speaks of *targeted* post-registration field research. This tends to be of a descriptive nature (monitoring) and must be regarded as being supplementary to earlier experimental research. The results will frequently exhibit a greater dispersion than pre-registration research, but they may, on the other hand, be able to give a better picture of the spatial and temporal variability in the behaviour of the substance and the occurrence of effects, especially if geostatistical techniques are employed. It is unclear, however, what role this information should play in decision-making for authorisation purposes. This is because there is still no spatial or temporal dimension in the government's protection objectives.

In order to validate the authorisation procedure, the Committee recommends that a finger should also be kept on the pulse in relation to authorised compounds by conducting research into the presence of plant protection products in environmental compartments (monitoring). This monitoring does not form part of the actual authorisation procedure and is not based on concrete suspicions. The Committee therefore speaks of *general* post-registration field research. The selection of the substances that are to be monitored can be based on the scale of use, toxicity, mobility or degradability. The substances that are selected will preferably include representatives from all of the important groups of substances. Indications of possible effects on organisms can be obtained by comparing concentrations that have been observed in the environment with (eco)toxicologically supported standards. In addition, it is possible to compare trends in the data collected by public and private bodies about populations of plants and animals with those relating to the use and the occurrence of plant protection products. This provides an indication of the potential role that these substances might play in a possible decline in population densities. This is, in fact, the only way to detect long-term changes. Additional experimental research is then needed in order to determine whether any causal connections exist.

Unsuspected harmful effects of plant protection products can also come to light as a result of sudden mortality (possibly on a massive scale) among conspicuous animal species, such as birds, fish or honeybees. The Committee advocates that a central research bureau should be established to investigate and record these ‘incidents’ and that this bureau should publish an annual report. It is not only important to investigate whether plant protection products are involved, but also whether these substances have been used as directed.

The results of general post-registration field research and incident investigations can be used in connection with the regular re-evaluation of substances or, in the case of serious suspicions, they can prompt immediate intervention in the authorisation process. This field research therefore forms a safety net for substances that have been wrongly authorised. Nevertheless, the Committee does not see any reason to subject the data that the applicant is required to provide to less rigorous requirements.

The Committee recommends that the results of field research that is carried out for the purposes of either the second tier (the pre-registration phase) or the third tier (the post-registration phase) of the risk assessment procedure should always be evaluated in connection with all previously available data. Although one can impose general rules with regard to the design and execution of field research, expert judgement will always play a role.

It is not only during the evaluation of individual substances that the results of field research are useful. They can also be used to improve the risk assessment procedure, especially the first tier. The Committee attaches great importance to research that is initiated specifically for this purpose. It can be used to validate, calibrate and (if necessary) improve fate models for the estimation of (exposure) concentrations in environmental compartments. It is also possible to evaluate both toxicity tests performed with standard test organisms in the laboratory and the applied safety factors for their suitability in estimating the risks in the field. A reliable first tier can frequently obviate the need for time-consuming and costly follow-up research for individual substances.

Chapter 1

Introduction

1.1 Background

The registration of pesticides for use in the Netherlands is regulated by the Pesticides Act (Stb98). Under this act, a pesticide can be authorised only if, when used as directed:

- it is effective for its intended purpose;
- it has no adverse effect on the treated crop;
- it does not present a threat to human health; and
- it has no unacceptable adverse effect on the environment.

This report is concerned with the last of these criteria.

Responsibility for registering pesticides on the government's behalf lies with the Board for the Authorisation of Pesticides (Dutch initials: CTB). The CTB evaluates the environmental risk associated with a given product based on data regarding the substance's physical and chemical properties, toxicity and means of application all of which are supplied by the party applying for registration (the manufacturer or importer). Using models which simulate the fate of pesticides in the environment, the CTB calculates the overall environmental concentrations of the substance likely to result from its use and the concentrations of conversion products likely to arise in various environmental compartments. The predicted concentrations are then compared with recent environmental criteria laid down in national and international laws and regulations. In principle, registration is withheld or withdrawn from substances and substance applications that do not meet these environmental criteria. However, an

applicant or registration-holder can appeal against an initial refusal to grant or renew a product's registration. To do so, he needs to provide rigorous additional research data demonstrating that the adverse effects forecast by modelling and laboratory tests would either not occur in practice, or would be reversible and short-lived. One way of obtaining such data is to conduct research in the field or in conditions that mimic those found in practice. In the past, field research has not always played a major role in the pesticide registration procedure. However, this situation may change now that legislation is in place that provides a more explicit legal framework. Various national and international bodies have drawn up guidelines for the design and conduct of various types of field research. In particular, the guidelines for research into aquatic systems, are quite detailed. Uncertainties nevertheless surround the interpretation of field test results — in other words, how the data obtained should be used when considering whether to register a substance. Given the high cost of conducting field tests, manufacturers also have a considerable interest in clarifying the principles on which interpretation is based.

1.2 Ministerial request for advisory report

The Minister of Health, Welfare and Sport asked the President of the Health Council to advise her and her colleagues, the Minister of Housing, Spatial Planning and the Environment, the Minister of Agriculture, Nature Management and Fisheries, the Minister of Transport, Public Works and Water Management and the State Secretary for Social Affairs and Employment, regarding how the results of field research could be used to assess the environmental risks associated with the use of agricultural pesticides. The full text of the Minister's request is reproduced in Annex A.

1.3 Composition and methodology of the Committee

On 22 April 1997, the President of the Health Council established the Committee on Pesticides and Field Research to deliberate on the issues for which the Minister was seeking advice. The Committee members are listed in Annex B.

The Committee examined various forms of field research and sought to determine the value of each for evaluating the risks associated with pesticide use. The Committee confined itself to plant production products*, since some of the recent additional regulations deal solely with these. Particular attention was focused on two broad categories of field research: that undertaken with a view to evaluating the acceptability

* The Pesticides Act (Stb98) distinguishes between plant protection products (substances for the protection or preservation of plants or vegetable products, substances that influence biological processes in plants [excluding fertilisers], weed killers and defoliants) and biocides (wood preservers, disinfectants, antifouling substances and substances that prevent organisms colonising buildings or control pathogenic organisms).

of new products, and that performed to determine the environmental prevalence and impact of plant protection products already in use. In accordance with the international literature, these two types of research are referred to in this report as pre-registration and post-registration field research, respectively. It is generally accepted that field research is valuable for the development and validation of models that simulate a substance's fate in the environment and for validation of the applicability of toxicity data from laboratory experiments; the use of field research for these purposes was not therefore considered closely by the Committee.

During its deliberations, the Committee reviewed all research that goes beyond standard single-species toxicity testing in the laboratory. On this basis, multi-species laboratory toxicity tests, research using artificial model ecosystems in the laboratory, in glasshouses or in the open air (divided on the basis of scale into microcosms and mesocosms), research involving (parts of) more or less natural ecosystems (including agro-ecosystems) and research for the purpose of studying pesticide behaviour in intact soil profiles were all considered. As all these types of study seek to reproduce field conditions more accurately, this report collectively refers to them as field research.

In recent years, various international bodies have published guidelines and protocols for the conduct of field research. However, few of these publications provide any real basis for the interpretation of research results when assessing a substance's acceptability. No detailed review of the international guidelines and protocols is presented in this report, but their common features are highlighted and the general requirements that field research should meet to effectively assess the risks associated with a particular substance are identified.

The Committee's conclusions are based partly upon the expertise of its members and partly on published academic literature. Consistency with the findings of previous Health Council Committees was also sought (GR88, GR94 and GR97a).

1.4 Structure of this report

Section 2 of this report contains a brief survey of the legislation and regulations relating to the authorisation of plant protection products. The survey is confined to those legal provisions relevant for the evaluation of risks such substances present for both non-target organisms and the environment. Particular attention is given to the legal scope for using field research to support such risk assessment.

Section 3 describes the plant protection product registration procedure that has been developed on this legal framework. Again, the emphasis is firmly on the nature and role of field research in this procedure.

Section 4 provides a more detailed examination of the requirements that pre-registration field research should meet to effectively contribute to the environmental

risk assessment associated with a plant protection product. Accordingly, consideration is given to issues such as the government's protection objectives, the resulting measurement endpoints, the statistical power of the research, and the relevance of the experiment to agricultural practice.

Section 5 is devoted to post-registration field research. Four main forms of study are discussed: targeted post-registration field research, the monitoring of plant protection product concentrations in environmental compartments, the monitoring of organism populations and incident research.

The concluding section of the report presents the Committee's advice regarding the use of field research in the risk assessment procedure with a view to efficiently determining with maximum certainty a pesticide's environmental impact.

A glossary of the abbreviations and technical terms used in this report is provided in Annex C.

Chapter 2

Legislation and regulations

Until recently, individual nations each had their own distinct pesticide legislation. As well as forming an obstacle to international trade, the transnational differences that existed tended to encourage the illegal use of substances that, although domestically not registered, were permitted in neighbouring countries. Pesticide manufacturers and importers also found it hard to accept that in every country where a substance was marketed, another different registration procedure had to be followed in full. For the last twenty years, therefore, the European Union countries have been working towards regulatory harmonisation based on directives which member states have to incorporate into national legislation. Pending European harmonisation, but also in line with EU regulations, the Dutch government has repeatedly amended national pesticide law in recent years. These amendments also relate to the requirements established to limit the environmental and ecological harm caused by pesticides.

This section of the report outlines the environmental criteria contained in Dutch and European regulations on the authorisation of plant protection products. Particular attention is given to the scope that the law allows for an applicant to use field research to secure registration on appeal, following an application's initial rejection on the basis of laboratory data and model calculations.

2.1 Dutch law

The registration of pesticides has been legally regulated in the Netherlands since 1947, when the Pesticides and Fertilisers Act came into force. This act, which was concerned

primarily with the effectiveness of substances sold on the Dutch market, was replaced by the Pesticides Act in 1962. It was this act that introduced the principle that registration of a pesticide should depend not only on its effectiveness, but also on the risks it posed to human health. In 1975, the act was amended to take account of the potential for harmful environmental side-effects.

The new criteria for the registration of a substance were set out in Section 3 of the act. However, lack of a clear definition for the concept of "harmful environmental side-effects" limited the practical impact of the 1975 amendments for a long time. As a result, environmental policy has not really been expressed within the pesticides registration procedure of the Netherlands (Eck95).

Between 1989 and 1991, operational environmental criteria were formulated (TK89, TK91a) and included in the Multi-year Crop Protection Plan (MJP-G) (TK91b). However, implementation of these criteria was blocked by the Business Appeals Panel, which ruled that assessment criteria contained in policy documents could not be considered to have force of law. In response, the Pesticides Act was amended once more. Section 3a was added, stipulating that a substance could only be registered if the substance and its conversion products complied with rules introduced by an Order in Council relating to the harmful side-effects referred to in Section 3 and to the impact of the substance on the quality of the soil (including groundwater), water or atmosphere. Article 3a is thus a hook on which to hang detailed registration criteria and standards (Eck95).

An Order in Council setting out environmental criteria in line with Section 3a came into force in February 1995. This order — the Pesticides Environmental Authorisation Requirements Decree (Stb95) — applies only to plant protection products, which can no longer be registered unless they comply with certain environmental criteria. Three of these criteria — those relating to persistence in the soil (Article 5), leaching into ground water (Article 6) and the risk to aquatic organisms (Article 7) are specified in some detail. Each of the articles 5 to 7 has four clauses. The first two of these clauses specify the actual environmental requirements (see table 1). The third clause describes the circumstances under which the requirements do not have to be met; in effect, this clause states that the requirements contained in clauses 1 and 2 should be regarded primarily as indicators of the desirability of further research. The fourth and final clause refers to a parallel Ministerial Regulation — the Regulation concerning the Application of Pesticides Environmental Authorisation Requirements (Stc98) — which details how the necessary tests and calculations are to be carried out and what constitutes compliance with the requirements. This regulation also indicates when data from field research can be used to determine compliance with the environmental criteria.

Table 1 The three environmental criteria against which plant protection products must be tested under Dutch law.

environmental criterion	environmental requirement
persistence in soil	DT_{50} < 90 days, soil-bound residues after 100 days ≤ 70% of the amount applied, in combination with mineralisation rate of ≥ 5% within 100 days
leaching into ground water	concentration in ground water < 0.1 µg/l or less than the toxicological standard if the latter is less than 0.1 µg/l, total concentration of simultaneously applied products < 0.5 µg/l
risk to aquatic organisms	peak concentration in surface water < 0.01 LC_{50} 'acute fish' and < 0.01 EC_{50} 'acute *Daphnia*' < 0.1 NOEC 'algae' average concentration in surface water over a given time interval < 0.1 NOEC 'chronic fish and *Daphnia*' and bioconcentration factor < 1000 for active ingredients that are readily biodegradable < 100 for active ingredients that are not readily biodegradable

Persistence in soil

If a substance is initially refused registration on the basis of Article 5, clause 1 or 2, of the Order in Council, Article 3 of the Ministerial Regulation allows the applicant or registration-holder two possible ways of obtaining registration on appeal:

- Field data may be submitted demonstrating that, contrary to laboratory test findings, under practical conditions the DT_{50}, the amount of soil-bound residues or the mineralisation rate would in fact meet the requirements.
- Evidence may be submitted, demonstrating that, although the DT_{50}, the amount of soil-bound residues or the mineralisation rate in the treated field would exceed the specified limit, this would not lead to a situation in which the maximum permissible concentration (MPC) for soil organisms is exceeded two years after the final application of the substance. An appeal on these grounds is only permitted, however, if the first-tier estimate of the DT_{50} is less than 180 days.

Leaching into ground water

Article 4 of the Ministerial Regulation stipulates how pesticide concentrations in ground water should be calculated. If calculations made on the basis of laboratory data indicate

that the concentration in the uppermost ground water will exceed the permitted level, the applicant can request recalculation based on data from field or lysimeter experiments (Annex IV to the regulation). Where a previously registered substance is being reassessed, monitoring data can also be used to demonstrate that the leaching requirement is met. Annex V to the regulation sets out the requirements that must be met by field research used to obtain data for these purposes. However, these requirements relate only to the quality of the research; nothing is stated regarding the quantity of data that must be obtained. Finally, if registration is initially refused because calculated or measured data indicate that the concentration in the uppermost ground water will exceed the permitted level, the applicant or registration-holder may appeal on the grounds of Article 6, clause 3, of the Order in Council and Article 4, clause 4, of the Ministerial Regulation. The provisions of these passages allow a product to be registered if it can be demonstrated that the concentration ten metres below ground level would meet the relevant criteria at the end of the four-year transportation period. This has to be demonstrated by means of incubation tests carried out in the laboratory using water-saturated subsoil material.

Risk to aquatic organisms

If registration is initially refused because of a substance's toxicity to aquatic organisms (Article 7, clauses 1 and 2, of the Order in Council), the applicant or registration-holder can appeal on the grounds that there will be no unacceptable direct or indirect impact on aquatic organisms (Article 7, clause 3, of the Order in Council). Impact is deemed unacceptable if the MPC for aquatic organisms is exceeded, unless additional data from an adequate risk evaluation can be provided indicating that the calculated exposure concentration or the effect concentration under field conditions should be amended (Article 5, clause 4, of the Ministerial Regulation). Guidance on interpretation of the phrase "adequate risk evaluation" is given in Annex VII to the regulation. Such an evaluation may be based on further laboratory research and/or on studies carried out in aquatic ecosystems or in models of such ecosystems, since the fate of a pesticide in the field and the actual level of exposure and sensitivity to it can differ from those observed under laboratory conditions. The annex also states that additional research can provide information "regarding the speed of recovery in the event of a partial reduction in densities. If an effect is partial, temporarily exceeding the MPC during a few hours or days does not necessarily have serious long-term consequences for populations of species such as crustaceans and algae". It follows that the scope for recovery may be considered when assessing the risk associated with a substance.

The environmental criteria described above take full account of the relevant European directives (see below). In the near future, further criteria relating to toxicity to non-target species will be added to the Order in Council (see table 2).

If a plant protection product meets all the environmental and other requirements, it is registered for a period of up to ten years (Article 5, clause 1, of the Pesticides Act). Usually, use of the substance is reviewed after five years. Periodic reviews of this kind enable any new information about the substance to be considered and allow for the substance to be assessed against any additional requirements introduced since its original registration.

2.2 Community law

The European directive on the harmonisation of plant protection product registration procedures, directive 91/414/EEC, dates from 1991 (EU91). The directive is based upon the precept that active ingredients should be assessed at community level, while member states remain responsible for the registration of commercial products (plant protection products) based upon these active ingredients. Although registration therefore remains a national matter, the directive introduces the principle of mutual recognition. In other words, if a substance is registered by one Member State, the other member states must follow suit, unless special national conditions justify withholding registration.

Annex I to the directive contains a list of approved active ingredients. In due course, it will be possible to register a pesticide for use in the European Union only if it is based upon (an) active ingredient(s) contained in the list. The list presently contains just a handful of ingredients, but by 2003 roughly eight hundred "existing" active ingredients (ingredients registered for use within the European Community before 25 July 1993) will have been assessed for inclusion. Active ingredients introduced to the market for use as pesticides since 25 July 1993 are regarded as "new" ingredients (see below).

When considering plant protection products for registration, national governments have to use a number of criteria detailed in Annex VI to the directive. Subsequently published as a directive in its own right (directive 94/43/EC, as amended by directive 97/57/EC), this annex is usually referred to as the Uniform Principles (EU94, EU97). These principles provide a common basis on which member states can assess and rule on the acceptability of a plant protection product — a prerequisite for mutual recognition. As well as rules for the evaluation of substances, the Uniform Principles provide guidelines for the decision-making process, known as registration criteria. These include a number of environmental criteria relating to a substance's behaviour in the environment and its effect on non-target species. The criteria of soil persistence, leaching into ground water and risk to aquatic organisms were used as the basis for those

contained in the Netherlands' Pesticides Environmental Authorization Requirements Decree. One discrepancy does exist, however: under the European rules, the concentration of a plant protection product in surface water may not exceed 0.1 times the EC_{50} for a species of algae, whereas the Dutch limit is 0.1 times the NOEC for the organism. Criteria are also given for the quality of surface water used in drinking water production and for air quality. The latter criterion aims to protect applicators and bystanders. The other environmental criteria, which are intended to limit the risks to non-target species, are briefly summarised in table 2. Annex II to directive 91/414/EEC lays down various prescriptions relating to the dossier that has to be submitted in support of a request for the inclusion of an active substance in Annex I. According to this annex, data may also be requested concerning the effect of the substance on sedimentary organisms (*Chironomus*) and aquatic plants (*Lemna*). However, the Uniform Principles do not include decision-making criteria for these organisms.

In principle, registration should be refused if a preliminary risk evaluation indicates that acute or chronic effects are likely, unless it can be clearly demonstrated by means of an adequate risk evaluation that, under field conditions, application of the plant protection product as directed would not have any unacceptable effects. However, no definition is offered for the phrase "unacceptable effects". It is these so-called "unless provisions" that allow an applicant to use additional data from laboratory or field research in support of an appeal against the initial rejection of an application. In Annex III to the Authorisations Directive (91/414/EEC), which contains prescriptions relating to the dossier that has to be submitted in support of an application for the registration of an plant protection product, frequent reference is made in connection with the conduct of field tests to the guidelines published by the EPPO*, the OECD** and the SETAC***.

Incorporation of directive 91/414/EEC into Dutch law entailed extensive revision of the Pesticides Act (Eck95). The amended act came into force on 1 March 1995. In addition, Orders in Council were used to implement certain elements of the directive. More technical and procedural matters were dealt with by means of Ministerial Regulations. The Uniform Principles (EU94, EU97) were implemented via an Order in Council effective since 1 September 1995. This Uniform Principles Decree (Stb97) covers plant protection products that are based on "new" active ingredients. Products based on "existing" active ingredients have to be assessed using the environmental criteria set out in the Pesticides Environmental Authorisation Requirements Decree, until the active ingredients have been reassessed at community level and included in the list of approved substances in Annex I to directive 91/414. Thereafter, products based on

* European and Mediterranean Plant Protection Organisation
** Organisation for Economic Cooperation and Development
*** Society for Environmental Toxicology and Chemistry

existing active ingredients will also be assessed in accordance with the Uniform Principles Decree (Eck95).

Table 2 Environmental requirements that, under the EU's Uniform Principles (EU97), plant protection products must meet in order to be eligible for registration. The environmental requirements concerning persistence in soil, leaching into ground water and the risk to aquatic organisms (see table 1) are also included in the Uniform Principles, but, in the interests of brevity, are not repeated here.

environmental criterion	environmental requirement
birds and other terrestrial vertebrates	estimated exposure $\leq 0.1 \times LD_{50}$ or LC_{50} (short term)
	estimated exposure $\leq 0.2 \times$ NOEC (long term)
	bioconcentraton factor (lipid-based) ≤ 1
honeybees	maximum application rate (g/ha) $\leq 50 \times LD_{50}$ (µg/bee)
beneficial arthropods	≤30% of the test organisms in a standard laboratoy test affected at the maximum suggested application concentration
earthworms	$PEC_{start} \leq 0.1 \times LC_{50}$ (short term)
	$PEC_{long\ term} \leq 0.2 \times$ NOEC (long term)
soil microorganisms	maximum effect on nitrogen- and carbon mineralisation 25% after 100 days

Chapter 3

The registration procedure

The various laws and directives find their practical expression in a registration procedure, which is operated by the Board for the Authorisation of Pesticides (Dutch initials: CTB), based in Wageningen. If a manufacturer or importer wants to have a new plant protection product registered for use in the Netherlands, or to extend an existing registration, an application has to be submitted to the CTB. A variety of data concerning the product must accompany the application, including its purpose and means of application, its physical and chemical properties, the applicable analytical techniques and its toxicity to various standard test organisms. These are the so-called dossier requirements. The application is only processed, once all the necessary data have been submitted. An assessment of a plant protection product's risk to the environment forms part of the registration procedure. To this end, the substance is examined against all the applicable environmental criteria (see chapter 2). However, once a product has been registered, it will not be examined against new environmental criteria until its next periodic review. This chapter of the report outlines the registration procedure, highlighting the opportunities that exist for the applicant to support an application with field research data.

3.1 Tiered risk assessment procedure

When a plant protection product is considered for registration, the CTB examines it against each environmental requirement using a tiered approach. The first tier is a relatively straightforward general check. The purpose of this is to quickly distinguish

between cases where sufficient certainty exists regarding the impact of the substance to allow registration to be granted or refused without detailed assessment, and cases where closer examination is required. Thus, the time-consuming and expensive full procedure only has to be followed where strictly necessary.

3.1.1 *The first tier*

For the first tier, the CTB utilises data provided by the applicant concerning the substance's physical and chemical properties (volatility, solubility in water and octanol, etc.), its degradability and its application method and rate. These data are then used to estimate persistence, the degree of leaching into ground water, the level of exposure of organisms in a variety of environmental compartments and the extent of bioaccumulation, on the basis of specific weather, soil and crop scenarios. These estimates are derived from models that simulate the environmental fate of substances. Work on the validation of these models is still in progress. Although the models used differ from one country to another, so-called FOCUS groups are working on harmonisation within the EU (FOC95, FOC96a, FOC96b). Data from the modelling exercise are then compared against the limits specified in the environmental criteria (see chapter 2).

To facilitate assessment of the risks to organisms in different environmental compartments, the applicant also has to submit information regarding the sensitivity of such organisms to the substance under consideration. This information is obtained from laboratory toxicity tests, which have to be carried out in accordance with detailed protocols such as the OECD guidelines. The tests involve exposing certain standard test organisms to increasing concentrations of the pesticide in order to determine the $EC(D)_{50}$, $LC(D)_{50}$ or NOEC. For the substance to obtain registration, the ratio between toxicity and exposure has to be within certain limits specified in the environmental criteria.

Given that the scenarios upon which the estimates are based involve quite extreme (i.e. unfavourable) environmental conditions, and that the specified limits include generous safety margins, it may reasonably be assumed that, if the modelling exercise suggests that a substance will meet the environmental criteria, its use will have no unacceptable impact in practice.

3.1.2 *The second tier*

Should the simulation models indicate that one or more of the limits would be exceeded, the application is not rejected outright. Rather, the applicant has the opportunity to appeal against the initial ruling within a specified period. To do so, additional data have

to be provided demonstrating that under practical conditions the limits will not be exceeded, or that infringement of the limits will have no unacceptable consequences (Kyl96). Thus, the second tier of the risk assessment procedure gives practical expression to the law's "unless provisions". If, when a previously registered product is reassessed, the model output suggests that the limits on toxicity to aquatic organisms or leaching into ground water are likely to be exceeded by a factor of up to 100, the registration-holder is given four years in which to obtain evidence refuting the findings. This dispensation is intended to take account of uncertainties in the modelling process. However, if the modelled levels exceed the limits by a factor of more than 100, the applicant has to be able to counter the findings immediately, or the product's registration is withdrawn. Before a new product can be registered then for each modelled limit infringement, the applicant has to provide detailed research data demonstrating that there would in practice be no environmental damage. For the assessment of leaching into ground water additional research may be required even if the model calculations show that the standard is met (concentrations in ground water between 1 and 0.01 times the standard) (Kyl96). This is justified by the fact that leaching model calculations are very sensitive to minor variations in the input data (DT_{50} and K_{om}).

For various environmental criteria the CTB has elaborated (the first and second tiers of) the risk assessment procedure in decision-making schemes (CTB99; see Annex D). The scheme for the criterion on the persistence of a substance in soil shows that two types of field research can be used to obtain additional data if modelling suggests that the limit will be infringed. These are studies to establish the rate of conversion in soil under field conditions (point 6 in figure 1) and field research to establish the concentration in the soil as a basis for determining the ratio of exposure to sensitivity of soil organisms (point 8 in figure 1).

Where additional data on leaching into ground water is required, field or lysimeter studies can be carried out (point 8 in figure 2). If the data thus collected fails to indicate that the modelled infringement is incorrect, breakdown in the saturated zone can be studied (point 10 in figure 2). This, however, is done in the laboratory.

If the registration requirement regarding the risk to aquatic organisms is not met, the first option open to the applicant is to calculate whether the MPC will be exceeded. If this proves to be the case, research can be carried out to establish whether the calculated exposure or effect concentrations require modification (point 7 in figure 3). This research may involve additional literature study, laboratory tests or field research on, for example, model ecosystems (microcosm or mesocosm research). Should modelling suggest that the bioconcentration factor (BCF) requirements will not be met, the applicant again has the option of carrying out additional field or other research in the second tier. Other environmental criteria contained in the Uniform Principles (see table 2) are also considered by the CTB as part of the risk evaluation (see figures 4 to 7 in

Annex D); in some cases, the possible impact on aquatic plants and sedimentary organisms is also taken into account. Data from field research can be used for the deliberation of these matters too. Annex E contains a summary of the various forms of additional (field) research that may currently be considered as part of the second tier of the risk assessment procedure. International efforts are currently being made to harmonise the guidelines covering these forms of field research (see, for example, Cam99).

3.1.3 The third tier

If, following the second tier of the procedure, doubts remain concerning the environmental impact of a plant protection product, the CTB can opt to limit the duration and geographical validity of the product's registration. This makes it possible to study the substance's environmental impact under practical conditions in the field. Once field data is available, the CTB can either register the product for general use or refuse registration altogether. Research of this kind, which may be regarded as an intermediate form between pre-registration and post-registration research, is an integral part of the registration procedure.

When reassessing previously registered substances, the CTB may also consider any field data on the substance, such as data from monitoring programmes or incident registration data. However, only data from field research that meets certain quality requirements can be used for this purpose. Based on such field research data, extension of a registration may be refused, granted, or granted subject to modified conditions. Finally, an applicant can be required to supply additional information if there is reason to suspect that the product may be harmful. Under exceptional circumstances, the CTB also has the power to modify a registration before the end of its period of validity. Field monitoring and incident research are not required by law and are not therefore integral parts of the registration procedure; such activities are undertaken on a voluntary basis.

Chapter 4

Field research prior to registration

No strict rules are laid down governing the organisation or performance of field tests, or concerning interpretation of the results. This is because the best approach varies considerably from one situation to another, depending on the research aim. Research intended to provide insight into a substance's environmental fate will differ substantially from, for example, research concerned with a pesticide's impact on a particular organism population or community. Much therefore depends on the judgement of people with the relevant expertise. Nevertheless, general guidelines are available covering various types of field test (see, for example, Ano91, Bar94, Cam99, Cro94, Som90).

When considering the main problems associated with the organisation and performance of field tests and the interpretation of field test results, the Committee restricted itself to a number of central issues that were considered relevant in relation to all types of research, irrespective of the environmental criterion involved. For (technical) details of the research forms in question, readers are referred to the above-mentioned guidelines. The most important question is what requirements a test should meet in order that the results may reasonably be regarded as "evidence" that the use of a substance would in practice have no unacceptable impact on environmental quality or on non-target organisms. Often, a party that intends to apply to have a plant protection product registered is well advised to submit a research protocol to the CTB for comment before starting the work. These issues are examined in more detail later in this section. First, however, the strengths and weaknesses of field research are briefly summarised.

4.1 Strengths and weaknesses of field research

Field research can provide valuable additional information about the behaviour and possible impact of substances under circumstances that more accurately reflect actual environmental conditions than those created for single-species toxicity tests in the laboratory (Bro93a, GR94, Mur87). A substance's fate in a field test — including its conversion, adsorption or transport — corresponds better with what happens in practice, and consequently such tests are better predictors of the exposure suffered by organisms in the environment. Furthermore, the behaviour of organisms in the field and in model ecosystems (micro- and mesocosms) is usually more natural. In the field, for example, an organism that is free to move around may be able to influence the exposure it suffers. Interaction can also take place between individuals within a population and between species. As a result, it is possible to study not only a substance's direct toxic effects, but also its indirect effects. Another advantage of field research is that data can be gathered regarding the sensitivity of species that cannot (easily) be kept in the laboratory. Most laboratory research is necessarily short term. In microcosms or mesocosms or in the field, on the other hand, one can carry out medium and long-term studies into, for example, deferred effects and recovery processes.

Some ecologists and ecotoxicologists believe that proper evaluation of the risks associated with xenobiotic substances is not possible without additional field research (Cai83). Others are more sceptical about the claimed ecological benefits, particularly of microcosmic and mesocosmic research. The sceptics argue that, because of its limited spatial and temporal scale, such research is liable to overlook or misconstrue important characteristics of communities and ecosystems and thus to produce misleading results (Car96, Sch98). The conclusion of this school of thought is that assessment should be based on "true" field research organised on a scale consistent with that on which environmental problems occur, and that semi-field research should be used for supplementary and support purposes only. However, the highlighted shortcomings of microcosmic and mesocosmic research really only affect studies of sizeable ecosystems, such as large lakes. Smaller ecosystems, such as ditches and soil ecosystems, are much easier to reproduce. Other authors have argued that an inductive step is always necessary in order to draw conclusions about natural ecosystems from data on the fate and impact of pesticides in model ecosystems. Although such a step is arguably smaller when using information from model ecosystems rather than from single-species toxicity tests in the laboratory, it still is necessary. However, since large-scale experimental research in natural ecosystems is often impractical and undesirable, tests using model ecosystems are generally the most realistic compromise (Cra97).

Despite the advantages described above, field tests do not in all cases facilitate the estimation of environmental risk and are not therefore always useful when assessing the risks of a pesticide. The greater realism that they provide comes at a price. Field tests are more complex and more difficult to control than laboratory tests and there is normally more variation between replicates; in consequence, interpretation of the data obtained is less straightforward. What is more, the cost of carrying out and evaluating a study rise rapidly as the size and complexity increase (GR94, Mur87). So much so, in fact, that in 1992 the competent authority in the United States, the EPA's Office of Pesticide Programs, decided to drastically reduce reliance on field test data for assessment of the risk to birds and aquatic organisms (Fis92, Tou97). This decision prompted a series of workshops and symposia, including a gathering organised by the Ecological Society of America (ESA), at which the value and practicality of field tests were discussed (Dae96, Sha96, Tau97). The predominant feeling was that, if properly organised and performed, field tests could make a valuable contribution to the ecotoxicological risk assessment of pesticides. This view is shared by the Committee. The Committee's thoughts regarding the organisation of field tests and ways of facilitating the interpretation of field test results are accordingly set out on the following pages.

4.2 Environmental protection objectives and acceptable effects

The Committee believes that a clear definition of unacceptable impact is a prerequisite for a meaningful test design and for the interpretation of the results in terms of a registration decision. A registration policy based upon impact assessment is not workable without clarity in this regard. The Committee would describe unacceptable impact as change that cannot reasonably be regarded as consistent with attainment of the government's environmental protection objectives, as expressed through the legally prescribed environmental criteria (see section 2). Unfortunately, the government's environmental protection objectives are not in all cases defined with sufficient precision. It is not clear, for instance, whether the government is committed to the protection of (local) species populations or merely the preservation of functional or taxonomic groups. The general efficiency of the registration procedure and, more particularly, the effective use of field tests for registration purposes depends upon a clear and unambiguous definition of the government's environmental protection objectives.

In order to decide whether an observed effect is acceptable, scientists need to translate the government's environmental protection objectives into manifest characteristics upon which research and assessment activities can focus. Such characteristics are referred to in this report as measurement endpoints. It is then necessary to indicate the ecological significance of certain changes in these measurement

endpoints and to draw a line between acceptable and unacceptable levels of change, with a view to facilitating realisation of the environmental protection objectives. To this end, close consultation between policy makers and scientists is essential.

4.2.1 Measurement endpoints

For assessment of the risk to individual species or the risks associated with leaching into ground water and persistence in soil, the selection of appropriate measurement endpoints is relatively straightforward. The process involved is exactly the same as in the first tier of the risk assessment procedure. Assessing the risk to an entire community is more difficult, however. The test organisms used for first-tier assessment are not themselves the species to be protected, or at least not the only species, but represent larger groups of organisms that require protection. Research into the impact on a community needs to be wider in its scope. Calow points out that the crux of the problem is lack of knowledge regarding ecological systems. Without knowing more about such systems, it is hard to formulate environmental protection objectives and, therefore, to choose measurement endpoints (Cal94). Some commentators have argued for research to concentrate on changes which are themselves the causes of change, in other words factors that compromise the resilience and stability of ecosystems. Understanding of the factors that determine ecosystem stability is increasing, but remains limited. The Committee believes that enough is now known about shallow freshwater ecosystems — and in particular the way they are affected by pesticides — to enable suitable measurement endpoints to be selected (see, for example, STO98a and STO98b). However, where certain other ecosystems, including terrestrial systems, are concerned, current knowledge is insufficient.

The Committee suggests that field tests set up to study the impact of pesticides on communities should initially concern themselves with structural measurement endpoints, i.e. taxa. Depending on what one is seeking to protect, research can focus on species, higher taxonomic groups (genera, families, orders, etc) or functional groups. Preferably, the taxa to be studied should be specified for each type of ecosystem — at least, each system which it is suspected may be at risk — on the basis of all available information regarding their sensitivity and significance for the stability of the ecosystem. To this end, generally acceptable guidelines should be drawn up (insofar as they are not already available). Where adequate scientific knowledge regarding an ecosystem is lacking, the Committee would advise studying a range of species:

- from various taxonomic groups
- from various trophic levels
- with various ecological functions

- with various life cycles.

(See also GR88, Jon95, Jon97.) These criteria are generally taken into account in the published guidelines for aquatic field research. The same also applies to the reported aquatic field tests (Bro94). The sex ratio, age profile or genetic constellation of a population can also be used as measurement endpoints if there is reason to suspect that changes sufficient to compromise the environmental protection objectives could be induced in these variables (see, for example, Dod99, Gut94, Sul99, Tak96).

In addition to taxa, research could concentrate on certain processes, such as the rate of photosynthesis, respiration, N-mineralisation, nitrification and so on. However, because of functional redundancy, some processes are less sensitive to particular pesticides than structural ecosystem characteristics, since they are maintained by several species. If one species disappears, another takes over its function (Bro93b, Ker94, Lev89, Pratt in Sut95).

4.2.2 Acceptable changes

Once appropriate measurement endpoints have been selected, it is necessary to determine what numerically expressed levels of change in these endpoints are consistent with realisation of the environmental protection objectives. Without some yardstick of acceptability, it is not possible to decide from the test results whether a substance should be registered or not. In this context, Calow states that at least the extinction of populations should be avoided. However, in the interests of the ecosystem as a whole, it may be necessary to maintain population densities and biomasses within certain limits (Cal94). Unfortunately, ecologists are in many cases, presently, unable to indicate what the ecological consequences of a given change are, and, therefore, how significant they are in relation to environmental protection objectives. Often, the way that change in a given endpoint is likely to influence other components of the ecosystem through the web of trophic and other relations, can be predicted only on a very general level, i.e. not in terms of the effect on individual species, but in terms of the effect on functional groups, (Bro93a, Cra97). Nevertheless, it may be assumed that indirect effects of this kind diminish as the intensity and duration of the direct effects decrease. The Health Council recently published a report summarising what is currently known about these matters (GR97a).

Little reference is made in ecotoxicological literature to the issue of ecological significance. Rather, the emphasis tends to be on statistical significance (Sut96), which is in effect a quantitative expression of the certainty with which an observed change can be attributed to the factor under consideration (in this case, the application of a plant protection product). Statistical significance does not, however, reflect the ecological

significance of the observed change. Hence, statistically significant effects are not *necessarily* of any great ecological importance. On the other hand, ecologically important changes may occur that do not result in statistically significant differences. This issue is considered more closely in subsection 4.3.

Lack of interest in the ecological significance of induced changes probably results from the fact that policy makers have tended to focus on no-effect levels (see Bru97). It is the Committee's belief that the absence of a yardstick of acceptability, on the basis of ecological significance, against which to measure effects is one of the major reasons for the ongoing disagreement regarding the interpretation of field test results. The Committee therefore believes that a scientifically justified acceptable degree of change should be specified for each measurement endpoint, possibly incorporating a safety margin.

In connection with a discussion about replacing the NOEC by an EC_x, Van der Hoeven and colleagues (Hoe97a) argue in favour of fixing the accepted effect, x, at 5 or 10 per cent of the value of the variable in question. However, they do not provide any ecological justification for this suggestion that is linked to environmental protection objectives. Ecologically speaking, it must be preferable to set a separate x-value for each measurement endpoint. After all, changes in variables such as oxygen production rate, water flea numbers and otter numbers are not necessarily of equal ecological significance simply because they are similar in percentage terms. The work of Domsch and colleagues (Dom83) may be instructive in this regard. This team suggested that the acceptability of an effect should be related to the extent of natural fluctuations in comparable systems that are not stressed by "anthropogenic" substances. In many cases, however, little data on natural fluctuations is available. By linking acceptability to natural fluctuations, a time factor is introduced into the definition of acceptability. This issue is considered in more detail below. Finally, non-ecological considerations, such as social and ethical principles, can play a part in the assessment of acceptability. So, for example, the "cuteness" of an organism can influence the way people feel about anything happening to it. In this context, readers are referred to the Health Council's report on principles for the protection of higher organisms against pollution (GR97c).

4.2.3 Recovery

One of the main advantages often ascribed to field research is that it enables scientists to study recovery processes, which can then be taken into account when making decisions about the authorisation of pesticides (Bro93a, GR94, Mur87). In principle, the Committee endorses the use of data on recovery processes in the decision-making process. The Committee regards changes that are reversed within a reasonable period as acceptable, since by definition they do not compromise environmental protection

objectives. However, populations, communities and ecosystems are historical structures; at any given point in time, these entities and their functions are a reflection of all prior influences (Lan97). One must therefore ask exactly what it is that returns to its former state, and whether the reversible changes are accompanied by permanent alterations which could threaten environmental protection objectives. Brock and colleagues (Bro93a) suggest that a population in a stressed model ecosystem may be regarded as having recovered if, following a significant increase or decrease directly or indirectly attributable to the stressor under study, the number of individuals returns and (for an extended period) remains within the normal distribution observed in the control systems. However, "recovery" of this kind does not necessarily imply that the populations and ecosystems involved return to exactly the same state as they would have been in when a contaminant never had been present. Changes may persist in, for example, the age profile of or sex ratio within a population, or in the allele frequencies (see, for example, Dod99, Gut94, Sul99, Tak96). Another Health Council committee has previously drawn attention to the potentially serious ecological consequences of changes in the population genetics characteristics (GR94). Furthermore, shifts can occur in the species composition within taxa, which may go unnoticed if the study does not differentiate between species (see, for example, Gid96). Functions and processes may be taken over by other species. Therefore, the situation that exists following recovery is likely to resemble the original situation — or, to be more accurate, an undisturbed control situation — more closely if the intervention is less drastic and of a shorter duration. Whether the new situation is acceptable or not depends partly on the "spread" within which the environmental protection objectives are defined and partly on the long-term significance of the changes induced in relation to the protection objective.

Recovery processes taking place within ecosystems can be influenced by both internal and external factors. Internally induced recovery involves population growth based upon reproduction amongst the individuals that survive the contamination. Survival can be due to possessing lower sensitivity or greater resistance, being in an inert state or taking refuge in a location that is free from or less seriously affected by the toxicant. Functions and processes can also recover as less sensitive or faster-recovering species assume the tasks previously performed by the affected species. Externally induced recovery arises via recolonisation from other more or less adjacent ecosystems. In field tests, externally induced recovery does not always take place, either because the test systems are isolated or because the tests do not continue for long enough. Brock and colleagues (Bro93a) illustrated this point using the freshwater shrimp *Gammarus pulex*, which, on becoming extinct within an isolated test system, cannot re-establish itself there, due to its inability to cross land. If the species is reintroduced by the researchers, it is possible to establish whether the quality of the environment has recovered sufficiently to enable the freshwater shrimp to survive. In cases such as this, insight into the ecology

and demography of the species in question and its habitat (in particular the degree of habitat isolation) is an absolute prerequisite for reliable estimation of the extent to which recovery is likely in practice.

In order to identify and track changes induced by the administration of a plant protection product, it is necessary to compare control systems with test systems. Such comparison is itself only meaningful if the research meets strict quality requirements, especially when the research is intended to demonstrate that modelled effects do not actually occur in practice. The most important of these requirements concerns the statistical power of the test; the less this power is, the greater a change must be before it is (statistically) discernible and the sooner recovery will be assumed to have taken place. This point is considered in more detail below.

4.3 Test design and data analysis

Strictly speaking, the research conducted by a registration applicant may be restricted to studying the behaviour or effect of a plant protection product used at the maximum recommended rate. However, the Committee would prefer to see (eco)toxicity tests designed on the multiple-concentration principle, whereby a control is compared with several different levels of exposure or rates of use. This would provide information on the consequences of users exceeding the maximum recommended usage rates and therefore on the reliability of the risk assessment. Such an approach would also indicate a permissible rate of usage in the event that the maximum recommended rate had an unacceptable impact, and would shed light on the risks associated with use of the same substance on other crops at other rates.

Data collected from field research is often analysed as follows. The effect of the various treatments on each measurement endpoint is separately compared with the control, and the null hypothesis — the hypothesis that the true effect* is zero— is tested in each case (typically using a significance level, α, of 5 per cent). If the null hypothesis is not rejected, it does not follow, however, that no effect has taken place. After all, numerous other hypotheses — such as that the true effect of the treatment is 25 per cent or 50 per cent — might not have been rejected on the basis of the data obtained either. Hence, there is always a range of hypothetical true effect values that are statistically consistent with the data obtained, i.e. a range of values which cannot be rejected upon testing (with α=5%). The full range of such values is the 95 per cent confidence interval for the true effect of the substance associated with the obtained data. In other words, one can be 95 per cent sure that the true (but unknown) effect of the substance lies between

* See definition of “true effect” given in the glossary (Annex C).

the upper and lower limits of that interval. The level of effect observed in the test lies on the centre line of the interval*.

The No Observed Effect Concentration (NOEC) is the highest test concentration whereby the confidence interval for the true effect includes the value zero. Hence, at this concentration, the null hypothesis of 'no effect' still stands. In other words, at the chosen significance level, the possibility cannot be excluded that the concentration's true effect is zero. However, the confidence interval will include both positive and negative values as well. These may be quite high. So a NOEC is not a concentration that we can be sure has no effect. Therefore, an increasing number of commentators have in recent years expressed doubts about the use of NOECs for risk evaluation purposes (Cha96a, Cha96b, Cha96c, Hoe97a, Hoe97b, Sut96).

The Lowest Observed Effect Concentration (LOEC) is the lowest test concentration whereby the confidence interval for the true effect does not include the value zero. Hence, at this concentration, it is highly likely that there is an effect. The confidence interval indicates the limits within which the true effect in all probability lies.

In the Committee's view, there is little point in reporting only the NOECs (or LOECs) established from toxicity testing. It is strongly recommended that the limits of the confidence interval should be indicated, since this provides information about the extent of the true effect. Comparing the extent with the maximum acceptable effect provides insight into the ecological significance of the true effect.

The question remains to be answered what effect on a selected measurement endpoint we would like to be able to detect. Naturally, it must be an ecologically significant effect (see subsection 4.2). The test should be designed so that there is a very good chance (an 80 or 90 per cent chance, for example) that, if a certain treatment actually has an ecologically significant effect, it will be detected, i.e. that the null hypothesis — the hypothesis that there is no effect — will be rejected. The ability of a test to detect the effect sought is referred to as its power. When the test is designed, the required power can be achieved by selecting an appropriate number of replications, given the selected significance value, α, and the (quantitative) data already available regarding variation in the measurement endpoint (see, for example, Hoe98, Sok94). If a NOEC is determined in this way, the confidence interval for the true effect is very unlikely to include an ecologically significant effect. In other words, the true effect of this concentration is not, in all probability, ecologically significant.

By trying to minimise the variation within the treatments, it is possible to limit the number of replications required per treatment to achieve the desired power (c.f. Wey98). This is easier if the test systems used are no larger than necessary, given the nature of

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* Provided that non-transformed data is used.

the research objectives. For aquatic field research, therefore, microcosms and small mesocosms (up to 25 m3) are preferable to large mesocosms (Cro94, Sha96). Careful sampling methods that take account of spatial variation within the test system should also be used. Geostatistical techniques are helpful in this regard (Gil97, Gro98). The use of smaller test systems and fewer measurement endpoints has the added advantage of releasing financial resources so that more replications can be performed per treatment. This results in more targeted research - one of the things called for at the international workshops on this subject (see, for example, Sha96).

Because of numerous statistical objections to seeking merely to establish NOECs, many biostatisticians prefer to analyse data from standard toxicity tests in the laboratory using regression-analysis techniques in order to establish EC_x values (Cha96a, Cha96b, Cha96c, Hoe97a, Hoe97b, Sut96). An EC_x with a low x-value (representing the accepted effect) can then be used instead of an NOEC. The Committee recognises the scientific superiority of this approach, but sees the problems associated with selection of an appropriate model for the dose-response relation as a major drawback, particularly where field tests are concerned (Cha96b, Hoe97b). This is because, in field and semi-field tests, all sorts of inter-species interactions and interactions between species and the substance under examination take place. These interactions reduce the likelihood of a clear dose-response relation being found for a particular measurement endpoint. Without such a relation, it is not easy to calculate an EC_x.

Another argument sometimes made against the use of EC_x values instead of NOECs is that it is unclear what value for x, the accepted effect, should be chosen (Bru97). However, the Committee does not regard this as a valid objection, since the interpretation of research results as a basis for plant protection product registration always involves some kind of judgement about what is and is not acceptable (see subsection 4.2).

In recent years, increasing use has been made of multivariate techniques, such as redundancy analysis and principal response curve analysis, for the examination of complex field test results (Bri96, Bri97, Bri99a, Ked97, Lan97, Sha96). The advantage of techniques such as these is that all the available data is considered simultaneously. They are very good for identifying the endpoints that exhibit the greatest response to the treatment. Once identified, these variables can be studied more closely using univariate techniques, as outlined above. Multivariate techniques can also be used to analyse temporal trends. The Committee accordingly regards multivariate techniques as a valuable supplement to the more commonly applied univariate analysis methods. Whatever method is used, however, statistical analysis must always be followed by ecological interpretation.

4.4 Impact to be expected in practice

The environmental and other conditions — climatic conditions, soil properties, water quality, hydrology, connection with the surrounding area and so on — under which a toxicant and an organism meet, have a major influence on the transportation and conversion of the toxicant in the environment (and hence on exposure to it and on its toxicity), as well as on the sensitivity of the organism and the scope for recovery within the population. As a result, these conditions determine the nature and scope of the effects and consequently the level of risk to a large extent. Careful consideration therefore has to be given to selection of the conditions under which a field test is conducted. The CTB is, of course, concerned not so much with the impact of a substance on a test site during a trial, but with the substance's impact on and around the many places where it will be used following registration. So it is important that the test conditions (the scenario) are designed such that conclusions about the risk under practical conditions can reasonably be drawn from the test results.

One option is to conduct a number of tests under different conditions or at various places. The actual number of tests conducted should depend on the spatial variability of the environmental conditions (soil type, etc) under which the substance will be used in practice. Decisions can then be based on the least favourable results or on a particular percentile. Use of a substance might also be permitted only under certain conditions. A multiplex approach would be viable for relatively simple field tests — into the fate of a pesticide, for example, or its effect on a particular species — but, for cost reasons, would not be suitable for large mesocosmic studies into a pesticide's impact on aquatic organisms.

Alternatively, one can use effect-conducive conditions to ensure that field test data provides a more suitable basis for general conclusions. The thinking behind adoption of a worst case approach of this kind is that, if no unacceptable effects are detected under the unfavourable test conditions, it is highly unlikely that such effects will occur in practice. However, it is important that worst case conditions remain realistic, reflecting the actual likelihood of numerous adverse factors coming in to play at once. Drukker & Van Straalen (Dru93) have indicated that the ecological vulnerability of organism populations is determined by their exposure, their sensitivity to the toxicant in question and their ability to recover. It follows that a realistic worst case situation should at least involve

- high levels of exposure for the test organisms. Hence, taking the directions for use into account (particularly the type of crop for which the substance is intended and the season in which it should be applied), the tests should involve use of the

substance at the maximum rate. It is also important that the biological availability is quantified and is not unnaturally low
- test organisms with high intrinsic levels of sensitivity
- test species with limited powers of recovery (i.e. those with a long life cycle, no resistant life stages and limited mobility).

When creating realistic worst case conditions, researchers can utilise the knowledge already available regarding other pesticides which work in a similar way and behave similarly in the environment. To check whether the conditions are actually effect-conducive, it is possible to set up a "positive control". A positive control involves the use of another substance that is known to have harmful effects. If a field test does not actually make use of realistic worst case conditions, it can still provide useful data, provided that the registration authority can deduce from the results what the effect under such conditions would be.

Researchers at the DLO Winand Staring Centre (STO98a, STO98b) have compared data from a large number of field tests in which the impact of plant protection products on stagnant and running freshwater ecosystems was studied. The tests in question were conducted in various parts of the world and involved a wide variety of communities. Nevertheless, different tests involving a particular substance and similar exposure regimes (single or repeated application) generally produced fairly consistent $NOEC_{eco}$ and $LOEC_{eco}$ values. However, the indirect effects associated with concentrations in excess of the NOEC/LOEC did differ in nature. The similarity between NOEC and LOEC values may indicate that the most sensitive organisms in comparable ecosystems are usually more or less equally sensitive to a given plant protection product. This supports the validity of extrapolation from critical threshold values ($NOEC_{eco}$ and $LOEC_{eco}$ values) established in field tests (STO98a, STO98b).

Chapter 5

Field research following registration

Once a plant protection product has been registered, its environmental impact under practical conditions can be studied in the field. Various forms of post-registration field research are considered in this section.

5.1 Targeted post-registration field research

After completion of the first two tiers of the risk assessment procedure, uncertainties may remain regarding specific points relating to a plant protection product's hazards. Under such circumstances, the authorities can grant temporary or limited registration, subject to the condition that the applicant studies the effect of the substance's use in practice (see also Jon95). The objectives of such research are determined by very specific questions regarding the substance's fate or its effect on organisms and communities, which were raised during the first two tiers of the risk assessment procedure. Research of this kind is therefore referred to in this report as targeted post-registration field research. The data obtained from targeted post-registration field research can be used to decide whether a substance's registration should be either extended or withdrawn altogether. Very little use has so far been made of this option. Very recently, however, temporary limited registration was given to the fungicide kresoxim-methyl, on the condition that the applicant studied leaching into ground water under practical conditions.

The strengths and weaknesses of targeted post-registration field research are summarised in table 3. It has already been pointed out that pre-registration field research

Table 3 The strengths and weaknesses of targeted post-registration field research.

strengths
close correspondence with practical conditions
scope for long-term study
scope for fairly large-scale study
provides greater insight into the influence of spatial and temporal variations in environmental and practical conditions on the behaviour and impact of plant protection products
weaknesses
substantial spread in the results
observational rather than experimental; causal relationships cannot easily be demonstrated

corresponds much more closely with practical conditions than the standard toxicity testing or modelling carried out in the first tier; targeted post-registration field research corresponds more closely still. Field research conducted under practical conditions can often be continued for longer periods than are viable for research using experimental systems. Because post-registration studies typically focus on quite specific issues, less work has to be done at each location, making it possible to include more locations in the research. Although this will increase the spread in the research results, it will also provide greater insight into the way that spatial and temporal variations in environmental and practical conditions influence the behaviour and effect of the substance under consideration. Geostatistical techniques can be very useful (Gil97, Gro98), especially in relation to:

- the quantification of spatial and temporal uncertainties
- optimisation of the location of observations in space and time
- the quantification of the impact of spatial and temporal uncertainties on model calculations or
- spatial inference, based on, for example, spatial interpolation.

Targeted post-registration field research can also be used to verify whether the pre-registration research did indeed simulate realistic worst case conditions. Furthermore, it is more likely that the chance coincidence of conditions will make it possible to observe uncommon effects.

One disadvantage of this kind of field research is that it is more observational than experimental; it is really a form of monitoring. Post-registration research is therefore unlikely to provide evidence of a causal relationship between the use of a plant protection product and a particular ecological effect. Hence, the results should be used only in conjunction with data from earlier experimental research carried out in the first or second tiers of the risk assessment procedure.

The question is: how should the information obtained regarding spatial and temporal variability be used when considering whether to register a substance. In this context, the Committee believes that it is necessary to determine the scale on which unacceptable effects on either environmental quality or organisms can be tolerated. The Committee regards this as a matter for the policy makers; at present, the question of scale is not addressed in the environmental protection objectives contained in the Pesticides Act.

Another way of accounting for spatial variability is to limit the scope of a product's registration. A number of plant protection products will shortly be labelled as suitable for use only on soils with a certain pH. In this way, substances that are not eligible for general registration can be allowed onto the market, or allowed to remain on the market.

Practical data on the use of a substance can be taken into account when re-evaluating previously registered products against new environmental criteria. Nevertheless, for the reasons set out above, the Committee views data of this kind as a useful supplement to information from experimental research conducted under more or less controlled conditions, rather than a replacement for such information. Practical data can, however, be used to guide experimental research.

5.2 General post-registration field research

The purpose of the registration procedure — and ecotoxicological risk evaluation in particular — is to prevent the unacceptable consequences of plant protection product use. However, one can never be sure that one has succeeded in preventing such consequences. In the past, there have been a number of cases where a pesticide was allowed onto the market, only for registration to be withdrawn later, when it became apparent that the product did after all have an unacceptable effect on either environmental quality or organism populations. Organochlorine compounds such as DDT are perhaps the most familiar example. At the time of their introduction, almost nothing was known about their bioaccumulation via the food chain, or about processes such as global fractionation and cold condensation, which cause these substances to migrate to and accumulate in the polar regions (Wan93). However, current-use plant protection products have proved to have unexpected properties as well. In the last ten years or so, for example, it has become clear that some of them can be dispersed atmospherically over large distances (GR00). And scientists have only recently become aware that some substances can act as hormone disruptors (GR97b, GR99). What is more, the behaviour and effects of a plant protection product can be modulated in unexpected ways by climatic influences, the simultaneous presence of other toxic substances and the existence of other stressors.

With a view to bringing to light any unexpected behavioural characteristics or effects that registered plant protection products may have, the Committee believes that

pesticide research should continue after registration, with particular emphasis on field studies into pesticide prevalence in the various environmental compartments. Research of this kind would provide insight into the fate of the ten million kilograms or so of plant protection products used in the Netherlands annually. Quite a lot of work in this field is already done in the Netherlands by organisations such as the National Institute of Public Health and the Environment (RIVM), the Institute for Inland Water Management and Waste Water Treatment (RIZA), the National Institute for Coastal and Marine Management (RIKZ), the Netherlands Organisation for Applied Scientific Research (TNO), provincial governments, water boards and water supply companies (see, for example, Bol94, Phe96, PZH94, Tas96). Since it is impractical to monitor all registered substances, the Committee recommends prioritisation on the basis of the scale of use, toxicity, mobility and degradability. Monitoring of representative substances from all the main pesticide groups is also advisable. Furthermore, by comparing measured concentrations with standards based on toxicological research, such as maximum permissible concentrations (MPC) and negligible concentrations, it is possible to pick up signs of any effects that might be taking place. If no evidence of unacceptable dispersal or effects has been found after a number of years, a substance should be withdrawn from the monitoring programme.

Spatial and temporal changes in the Netherlands' animal and plant populations have in recent decades been monitored by numerous governmental and non-governmental bodies. Those involved include provincial governments, water boards, FLORON (Foundation for Floristic Research in the Netherlands), SOVON (Dutch Centre for Field Ornithology) and the Dutch Butterfly Conservation. This research provides valuable data and makes it possible to investigate the possible role of plant protection products in any population decline (Gre92, Ril90, Som90). One practical shortcoming of the work carried out to date is that studies have tended to focus on biologically interesting areas, rather than on agricultural areas. In other countries, population monitoring has proved valuable — revealing, for example, that pesticide use may be responsible for the decline of certain bird species in Great Britain (Cam97). However, further (experimental) research is required before conclusions may be drawn regarding the existence of a causal relationship or regarding the mechanisms involved. In many cases, a population decline is attributable to a combination of factors, making it hard to establish what role, if any, a plant protection product has played. Post-registration population monitoring can be particularly helpful in connection with species which were not the subject of any pre-registration studies or incident investigation. The strengths and weaknesses of general post-registration field research are briefly summarised in table 4.

Being by definition non-targeted, the detection of unexpected behaviour or effects is not part of the pesticide registration procedure. Such work would seem to be predominantly a task for the government. Nevertheless, data from such research can be

Table 4 The strengths and weaknesses of general post-registration field research.

strengths
close correspondence with practical conditions
scope for large-scale study
provides information on the dispersal of plant protection products in the environment as a function of space and time
scope for very long-duration study; provides information on long-term influence on organism populations
provides an integrated picture of the influence of all human activities on organism populations
weaknesses
effects can only be detected by reference to detailed information on organism population trends
the influence of plant protection products is hard to distinguish from the influence of other human activities or natural stressors
observational rather than experimental; causal relationships cannot easily be demonstrated

included in (decennial) reassessments or used as a basis for immediate intervention in cases where serious suspicions exist. Intervention should be considered, however, only if the unexpected effects are known to occur when the substance is used according to the legal directions; intervention is inappropriate where effects are attributable to inappropriate, improper or illegal use. Information obtained from post-registration monitoring can also be used to improve the registration procedure so as to prevent the future registration of substances with similar harmful effects.

Unexpected behaviour and effects are not the only matters that are difficult to study in the context of a registration procedure. Very gradual changes which become apparent only over extended periods come into this category. During the course of a field test, typically lasting no more than a year, a marginal drop in the number of individuals in a population may, for example, go unnoticed, i.e. be statistically insignificant. However, if such a fall were to be repeated year after year as a result of consistent use of a pesticide, it could ultimately lead to a substantial reduction in or even the extinction of the population in question. Furthermore, a repetitive cycle involving the death of a (significant) proportion of a population following pesticide use, followed by rapid recovery, can bring about marked genetic selection. The consequent decline in genetic diversity, possibly accompanied by a reduction in ecological fitness, could undermine the resilience of a population (Gut94, Sul99). The importance of research into population genetics was highlighted in an earlier Health Council report (GR94).

Research into the long-term effect of a pesticide is in the Committee's view best conducted at sites where the pesticides are in intensive use, since it is reasonable to suppose that any impact will be discernible at such sites before it becomes apparent

elsewhere. Although data from research of this kind is unlikely to lead to the amendment or withdrawal of a product's registration, it can help to perfect the registration procedure.

5.3 Incident and enforcement investigations

Incident investigations do not involve actively monitoring the behaviour or effect of a plant protection product in the environment. Such research cannot therefore be used for registration purposes. Incident investigations entail responding to incidents such as the sudden extermination of plants or animals, by seeking to establish whether a plant protection product was (partly) responsible and, if so, which one. It is also possible to examine the conditions under which the incident occurred and to estimate the likelihood of repetition. Finally, it is important to ascertain whether each reported incident is the result of legal use of the substance in question, or of improper or illegal use*. The strengths and weaknesses of incident investigations are summarised in table 5 (see also Som90).

In the Netherlands, incident investigations are conducted on an *ad hoc* basis only; the Agricultural Research Department - Institute for Animal Science and Health (ID-DLO) looks at incidents involving birds, while the Association of Water Boards looks at incidents involving aquatic organisms. The General Inspection Service (AID) of the Ministry of Agriculture, Nature Management and Fisheries also investigates certain incidents (involving bees, for example), but only where there are grounds to suspect that there has been a breach of the law. This work is referred to as enforcement investigations. The AID can curtail an investigation at any point if it becomes apparent that no offence has been committed. If an investigation is concluded at an early stage, the opportunity to obtain information that might have been useful for the registration procedure in general and, more particularly, for registration of the substance in question will be lost.

In the United Kingdom, incident investigation and registration are centralised. In 1997, 607 incidents were recorded, the vast majority involving vertebrates and a few involving bees (Fle98). Some 30 per cent of incidents proved attributable to pesticides; of these, 68 per cent were the result of deliberate poisoning, about 12 per cent were due to misuse or careless use, and 3 per cent to use for approved purposes. A total of 33 plant protection products were involved in the incidents. Recently published data from other European countries, including the Netherlands, shows that deliberate poisoning is

* The phrase "illegal use" is here intended to mean use of a substance that is not registered in the Netherlands, or use of a registered substance in a manner contrary to the legal directions for use. Either course of action is against the law. The phrase "improper use" is here intended to mean the use of a registered substance in accordance with the legal directions, but contrary to the manufacturer's advice. Improper use is not illegal. See Hor95.

Table 5 The strengths and weaknesses of incident investigation; see also Som90.

strengths
efficient way of detecting unexpected effects, which can then be studied more closely
close correspondence with practical conditions
opportunity for detection of improper and illegal use
effects on rare species can be studied if deaths occur
weaknesses
only effective if people are generally prepared to report incidents
small ‘inconspicuous’ species are frequently overlooked
species that leave the application area are less likely to be found
concerned primairily with fatalities; more subtle effects are overlooked
only effective in connection with products that leave residues in the tissues of dead organisms or which cause recognisable (pathological) symptoms

also the principal cause of sudden deaths in mainland Europe (Sno99). The use of pesticides for approved purposes was only a factor in a minority of cases (less than 20 per cent). Illegal or improper use cannot be prevented by modifying a product’s registration, but may lead to stricter or more targeted supervision by bodies such as the AID and to special public information campaigns.

Incident investigation can lead to the detection of unexpected effects. This was seen in the Netherlands during the summer of 1996, when there was a sudden large-scale bee extermination associated with the legal use of a substance called dimethoate to kill aphids in potato fields. Because of the general scarcity of flowers, bees were attracted to potatoes, a crop they normally find unattractive, to “milk” the aphids. To reduce the risk to bees in the future, the legal directions and the advice given to users of anti-aphid products were amended (CTB98). In previous incidents, bird deaths caused by pesticides for the treatment of seeds and insecticides developed to kill larvae of the crane fly have led to the amendment of product registrations.

The Committee recognises that, with the exception of careful bee monitoring by beekeepers, incident investigation is effective almost exclusively in connection with “conspicuous” animals — primarily vertebrates. However, these species are very rarely included in research based on model ecosystems. Hence, incident investigation is an efficient way of obtaining information that would not otherwise be readily available. The Committee would therefore like to see the establishment of a central agency to investigate all incidents, to look into the possible role of plant protection products in such incidents, to determine whether the incidents involve legal, improper or illegal use, to record incident data in a databank and to issue annual reports.

By way of conclusion, the similarities and differences between the various forms of post-registration field research are summarised in table 6.

Table 6 Distinctions between the various forms of post-registration field research.

question	*targeted research*	*general research*	*incident / enforcement investigation*
who is responsible	manufacturer	government	government (AID)
which substances are concerned	substances selected on the basis of the 1st and 2nd tier	substances selected on the basis of extent of use, toxicity, mobility, degradability and category	substances selected on the basis of incident profile
what is studied	anticipated effects	unexpected effects	incidents
what is studied	fate of substance and/or biota	fate of substance and/or biota	biota, sometimes fate of substance
what kinds of use are considered	legal, proper use	legal, proper, illegal, and improper use	legal, proper (incident investigation), illegal and improper use (enforcement investigation)
which organisms are involved	usually common species found on agricultural land, both conspicuous and inconspicous	common and rare species found on agricultural and non-agricultural land, both conspicuous and inconspicous	common and rare species found on agricultural and non-agricultural land, conspicuous species only
where	near application area	near application area and further afield	at incident location
how many locations	a small number	a larger number	depends on number of similar incidents
duration	one or two years	several years	a short incident-determined period (a few weeks)
integral part of registration procedure	yes	no	no
why	to remove remaining doubts regarding acceptability of effect	to verify effectiveness of risk assessment and directions for use	to verify effectiveness of risk assessment and directions for use

Chapter 6

Concluding remarks

The best way to reduce the harm that plant protection products cause to the environment and to human health is to limit their use. As the Multi-year Crop Protection Plan indicates, the government is committed to doing just that (TK91b). However, where pesticide use is necessary for agricultural or health reasons, the safety of these substances should be investigated as thoroughly and as efficiently as possible. A tiered registration procedure provides the best context for such investigation. The various forms of field research described in this report all have their own place in this procedure and their own contribution to make to efficient and reliable risk evaluation (see figure 8 and Jon97).

However, field research has one important function that this report has so far barely touched upon, namely improvement of the first tier of the risk evaluation procedure. The results of research conducted for this purpose can be used to validate, calibrate and, where necessary, improve models for the estimation of (exposure) concentrations in the various environmental compartments. It is also possible to use field research data to assess the suitability for risk assessment purposes of safety factors and of laboratory toxicity tests involving standardised test organisms (see also Jon95). A good example of this involves a recent study of the ecological risks associated with the presence of herbicides in freshwater ecosystems (STO98a). Evaluation of field test results published in the scientific literature revealed that first-tier risk assessment based on the toxicity of substances to water fleas, fish and algae did not always result in adequate protection for macrophytes against auxin-simulating herbicides. The researchers accordingly suggested

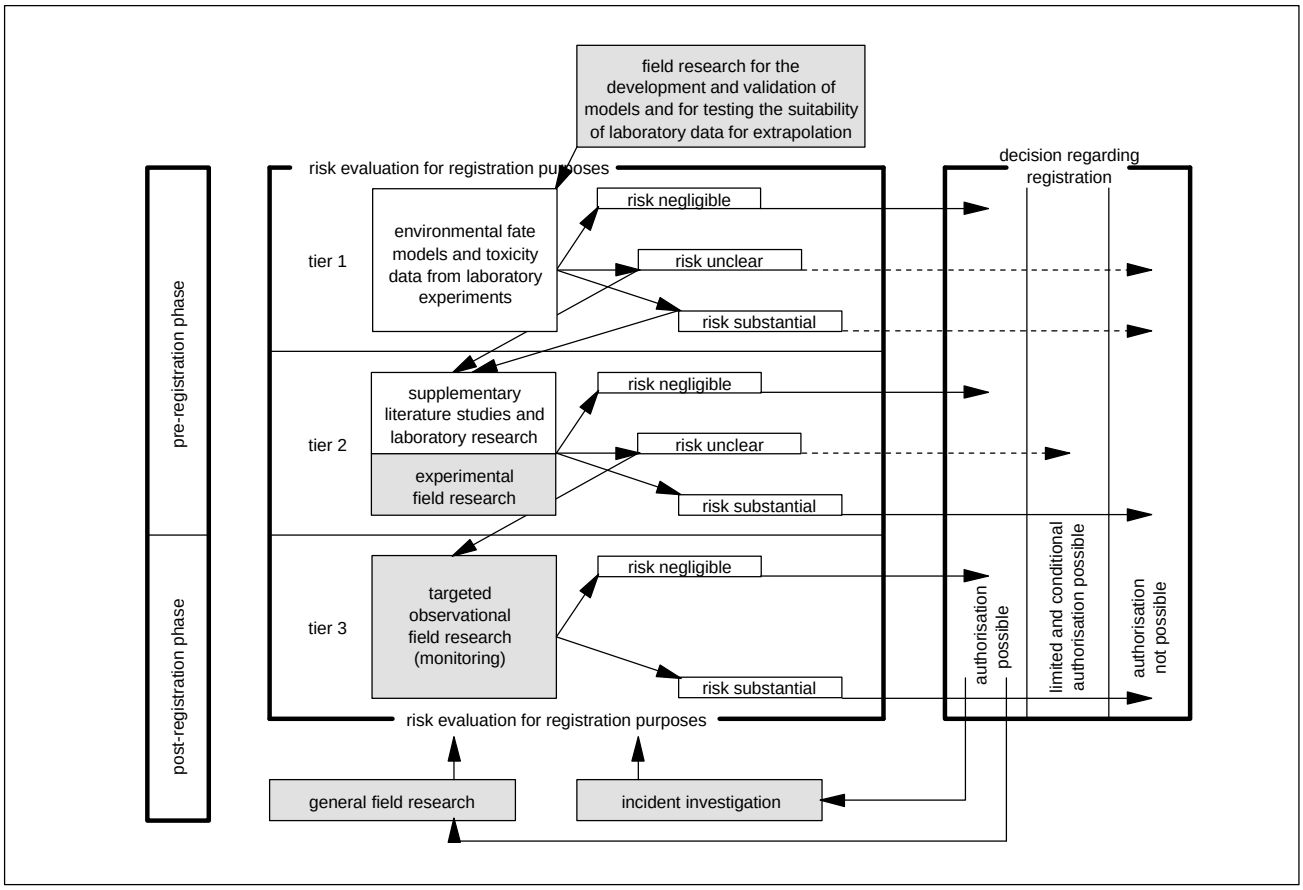

Figure 8 The possible role of field research (shaded areas) in the assessment (for registration purposes) of the environmental risks associated with the use of plant protection products. The arrows with the dashed lines indicate the possibility of reconsidering the authorisation decision on the basis of additional research data provided by the applicant.

the risk evaluation of auxin-simulating herbicides should include toxicity tests on higher, rooting water plants. Other researchers have compared the results of standard laboratory toxicity tests with field test data (ECE97, Ham96, STO98b). Generally speaking, the criteria used in the first tier are more than adequate for evaluating the risks associated with plant protection products. In other words, the first tier may on the whole be regarded as strict.

The Committee would like to see the results obtained from research conducted in later risk evaluation tiers compared with data obtained in the earlier tiers, and with results of research into other substances which work or behave in a similar way in the environment. Any differences detected should be explainable and interpretable. Thus, the final decision regarding a product's registration should be based upon all the available information. In this, the judgement of experts inevitably plays a key role.

According to some researchers, where post-registration field research is effective, the requirements regarding the data that an applicant has to provide with a registration application could be made a little more flexible, particularly with regard to matters such as the number of locations at which research has to be conducted (Som90). The calls for greater flexibility do stress that a more supple approach would be appropriate only subject to strict conditions and where the risks were considered slight. Nevertheless, the Committee would not support any relaxation of the requirements, partly because all forms of post-registration field research have certain limitations, and partly because preventive action is always to be preferred to curative action.

on behalf of the Committee
The Hague, 14 March 2000

signed

Dr HFG van Dijk,	Professor dr L Brussaard,
Scientific secretary	Chair

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B The committee

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D CTB decision-making schemes

E Forms of supplementary pre-registration (field) research

Annexes

Annex **A**

Request for advice

On 15 April 1997, the Minister of Health, Welfare and Sport wrote as follows to the President of the Health Council (letter reference GZB/C&O/971541):

On 13 February 1996 (DGVgz/VVP/C951554), I wrote to you asking that the Health Council prepare reports for myself and my colleagues, the Minister of Housing, Spatial Planning and the Environment, the Minister of Transport, Public Works and Water Management, the Minister of Agriculture, Nature Management and Fisheries and the State Secretary for Social Affairs and Employment, concerning pesticide risk assessment. In my letter, I indicated that during the course of the project a number of priority issues would be identified for closer consideration.

Since then, you have produced the first report in this context of pesticide risk assessment concerning the ecological consequences of pesticides in ground water.

I now wish to hear your views on the way field tests may be used for assessment of the environmental risks associated with pesticides.

Field research will in future play an increasingly important role in environmental risk assessment for the purpose of pesticide registration. As well as being useful for the constant validation and refinement of risk estimation models, field research can be a valuable tool for the authorisation of single products. The Pesticides Environmental Authorisation Requirements Decree provides for the use of field research as a basis for revision of the initial risk assessment based on laboratory test data and model output. The monitoring of pesticide concentrations in the environment, typically undertaken by governmental organisations or interest groups, is also a form of field research. Provided that monitoring meets certain quality requirements, the results can be used when considering the extension of an existing pesticide registration.

In terms of complexity, laboratory toxicity tests involving a single species of test organism and field research into the impact of contaminants on ecosystems are opposite extremes. Many intermediate forms of research are possible and are already used to facilitate prediction of the environmental impact of pesticides under natural conditions. Such intermediate forms include multi-species laboratory tests and studies conducted in the laboratory or out of doors using model ecosystems of various sizes (microcosms and mesocosms).

In your report, I would like you to summarise the experience so far gained with these different forms of laboratory and (semi-) field research, and to indicate whether and, if so, how they can be formally integrated within the registration procedure.

[signed]
Dr E Borst-Eilers,
Minister of Health, Welfare and Sport

Annex **B**

The committee

- Dr L Brussaard, *Chairman*
  Professor of soil biology and biological soil quality; Wageningen University
- F Baerselman, *adviser*
  Ministry of Agriculture, Nature Management and Fisheries, The Hague (until 1 March 1998)
- Dr TCM Brock
  Ecologist; ALTERRA, Wageningen
- Dr E van Donk
  Professor of limnology; University of Nijmegen; also Netherlands Institute of Ecology, Centre of Limnology, Nieuwersluis
- MA van der Gaag, *adviser*
  Ministry of Housing, Spatial Planning and the Environment, The Hague
- Dr CAM van Gestel
  Ecotoxicologist; Vrije Universiteit, Amsterdam
- Dr H de Heer, *adviser*
  Ministry of Agriculture, Nature Management and Fisheries, The Hague (from 1 March 1998)
- Dr N van der Hoeven
  Biostatistician; ECOSTAT, Leiden
- FMW de Jong
  Environmental biologist; Centre of Environmental Sciences, University of Leiden

- AMA van der Linden
  Soil chemist; National Institute of Public Health and the Environment, Bilthoven
- Dr PCM van Noort
  Environmental chemist; Institute for Inland Water Management and Waste Water Treatment, Lelystad
- Dr PA Oomen, *adviser*
  Plant Protection Service, Wageningen (from 20 September 1997)
- Dr A Stein
  Professor of spatial statistics; ITC, Enschede; also Wageningen University
- Dr LEM Vet
  Professor of entomology; Wageningen University; also Netherlands Institute of Ecology, Nieuwersluis
- PJM van Vliet, *adviser*
  Board for the Authorization of Pesticides, Wageningen
- Dr HFG van Dijk, scientific *secretary*
  Health Council, The Hague

Secretarial support: J Hoorens v/d Berg-de Vlieger
Layout: J van Kan

Annex **C**

Glossary

active ingredient

The component of a pesticide which is toxic to the target organisms; in addition to one or more active ingredients, a pesticide will usually contain various other substances, such as solvents, adhesives, spreaders and so on.

bioconcentration factor (BCF)

The ratio between the concentration of an active substance in an organism and the concentration in the medium (e.g. water) in a state of equilibrium.

95% confidence interval

The true value of a given parameter is not normally known. However, it can be estimated by taking a limited number of measurements. The 95% confidence interval is the range of possible parameter values that are statistically consistent with the results of the measurements, i.e. that cannot be rejected upon testing with $\alpha = 5\%$. See also “true effect”.

DT_{50}

The time required for conversion of 50 per cent of an amount of a substance in a given environmental compartment or test system.

EC_x

The concentration of a substance at which x% of the test organisms under study show an effect, or at which the test organisms show an average effect of x%.

environmental protection objective

An explicit definition of the environmental or ecological characteristic to be protected; the focus of risk assessment and management activities.

K_{om}

Degree to which a substance adheres to organic material in the soil.

LD_{50}

Application rate of a substance, at which 50 per cent of the test organisms under study die.

LOEC

Lowest Observed Effect Concentration: in a toxicity test, the lowest test concentration at which a statistically significant effect on the selected measurement endpoint is observed and at which the null hypothesis (the hypothesis that there is no effect) is therefore rejected.

lysimeter

Experimental apparatus in which the movement of water and solutions through soil can be studied. The distinguishing characteristic of a lysimeter is that the percolate can be quantitatively collected. Lysimeters are usually set up out of doors.

measurement endpoint

A measurable ecological characteristic associated with the environmental protection objective.

mesocosm

See model ecosystem.

microcosm

See model ecosystem.

mineralisation

The conversion of a substance into inorganic substances, which may be regarded as end products of the conversion process in the environment.

model ecosystem

Model ecosystems — also referred to as microcosms or mesocosms, depending on their size — are manmade, spatially delimited systems. They consist of elements of natural ecosystems or are created in the field by isolating parts of natural ecosystems with as little disruption as possible (enclosures). Model ecosystems are normally smaller and less complex than natural systems. However, they do contain a community of organisms that exists in "dynamic" equilibrium with its immediate surroundings and comprises several trophic levels (including primary producers, herbivores, detritivores and carnivores).

MPC

Maximum Permissible Concentration: the concentration of a substance in an environmental compartment, at which the risk to the organisms in that compartment is at the maximum permissible level. Where pesticides are concerned, the CTB is responsible for setting MPC values on behalf of the government.

NOEC

No Observed Effect Concentration: in a toxicity test, the highest test concentration at which no statistically significant effect on the selected measurement endpoint is observed and at which the null hypothesis (the hypothesis that there is no effect) is therefore not rejected.

PEC

Predicted environmental concentration: the forecast concentration in a given environmental compartment.

power

The likelihood of a true difference of a particular degree in the effect of two treatments being detected; equal to 1-β, where β (also referred to as the type II error) is the likelihood that a true difference of a particular degree in the effect of two interventions will go unnoticed, i.e. that the null hypothesis (the hypothesis that there is no effect) will be erroneously accepted.

risk

The possibility, with a certain degree of probability, of harm to health, the environment or property, in combination with the nature and extent of such harm.

significant

Attributable with a particular degree of confidence (1-α) to the intervention, where α (also referred to as the type I error and generally set at 5 per cent) is the likelihood that the null hypothesis (the hypothesis that there is no effect) will be erroneously rejected.

soil-bound residue

Residue in the soil, originating from the use of plant protection products, which cannot be extracted using techniques that do not affect the chemical nature of the residue.

tiered risk assessment procedure

A risk assessment procedure divided into several tiers (stages). The next tier is only proceeded to if the previous tier provides insufficient certainty regarding a substance's harmlessness.

true effect

The aim of a toxicity test is always to determine the true (toxic) effect on a given measurement endpoint of a treatment with a certain amount of the substance under study. The true effect can be regarded as the difference between the mean value of the measurement endpoint in an infinite number of control systems (test systems in which no intervention takes place) and its mean value in an infinite number of treated test systems. In practice, however, an experiment can only involve a (very) small number of control and treated systems. One is, as it were, obliged to draw random samples from the hypothetical populations of all the control and intervention systems that could be created. As a result, the observed effect is not only determined by the (unknown) true effect, but also by the random nature of the "sampling". In other words, the observed effect is merely an estimate of the true effect; if another test were conducted, it would (normally) result in a (slightly) different estimate. The precise extent of the true effect remains unknown at the end of the experiment, but one is able to indicate on the basis of the measured data how reliable the estimate is. See also the definition of "95% confidence interval".

Annex **D**

CTB decision-making schemes

See schemes on the following pages.

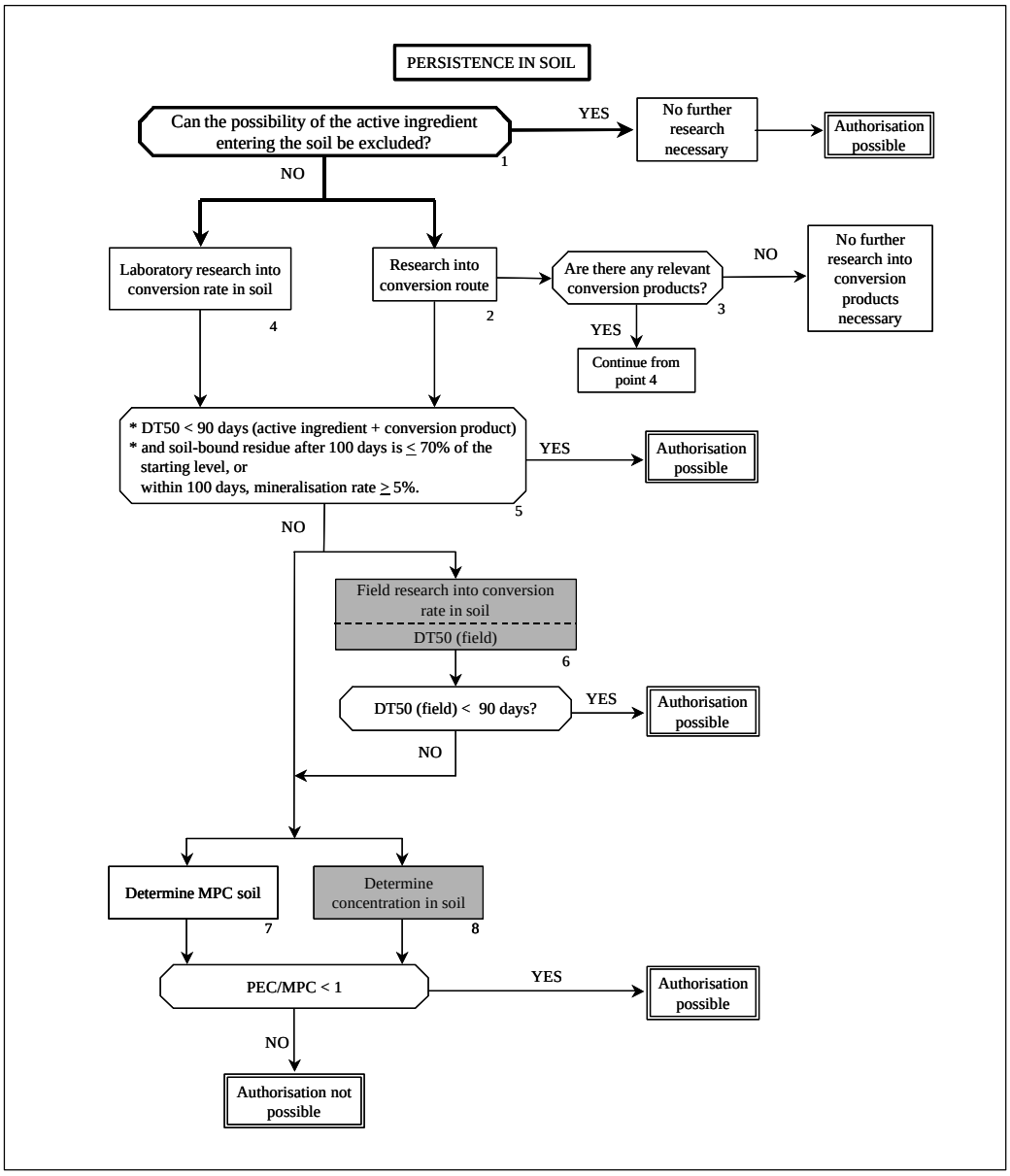

Figure 1 Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning persistence in soil (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

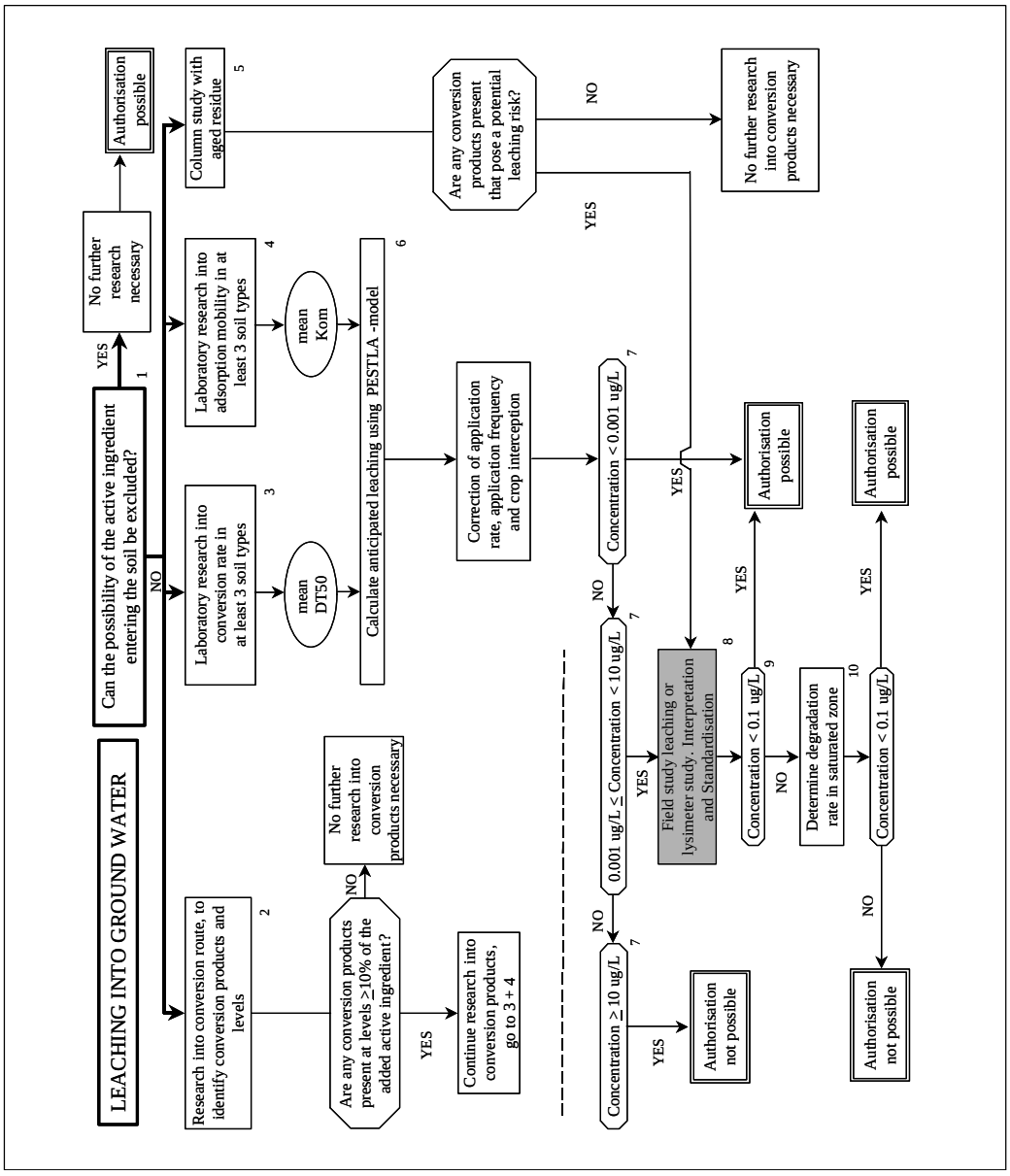

Figure 2 Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning leaching into ground water (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

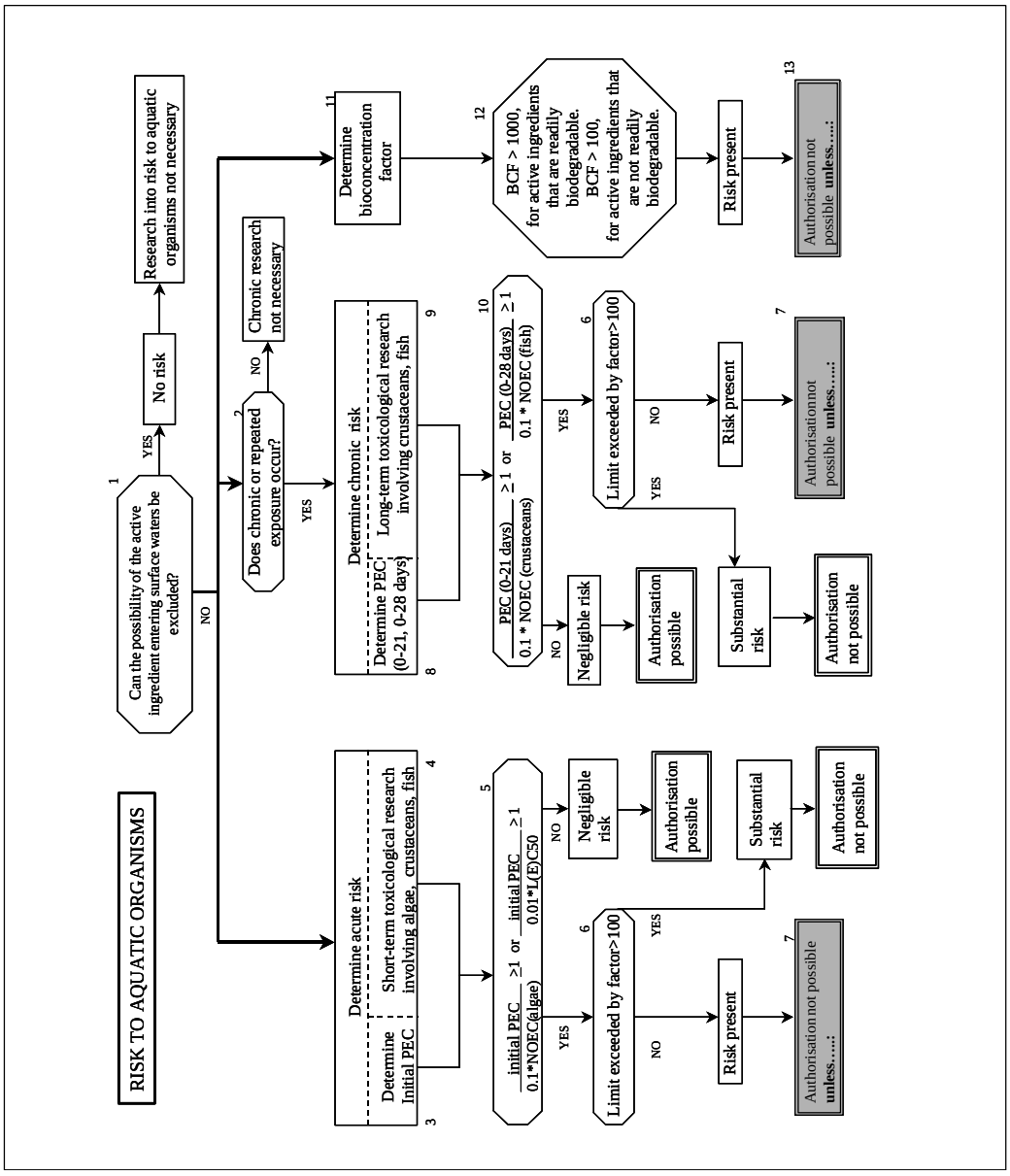

Figure 3 Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning the risk to aquatic organisms (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

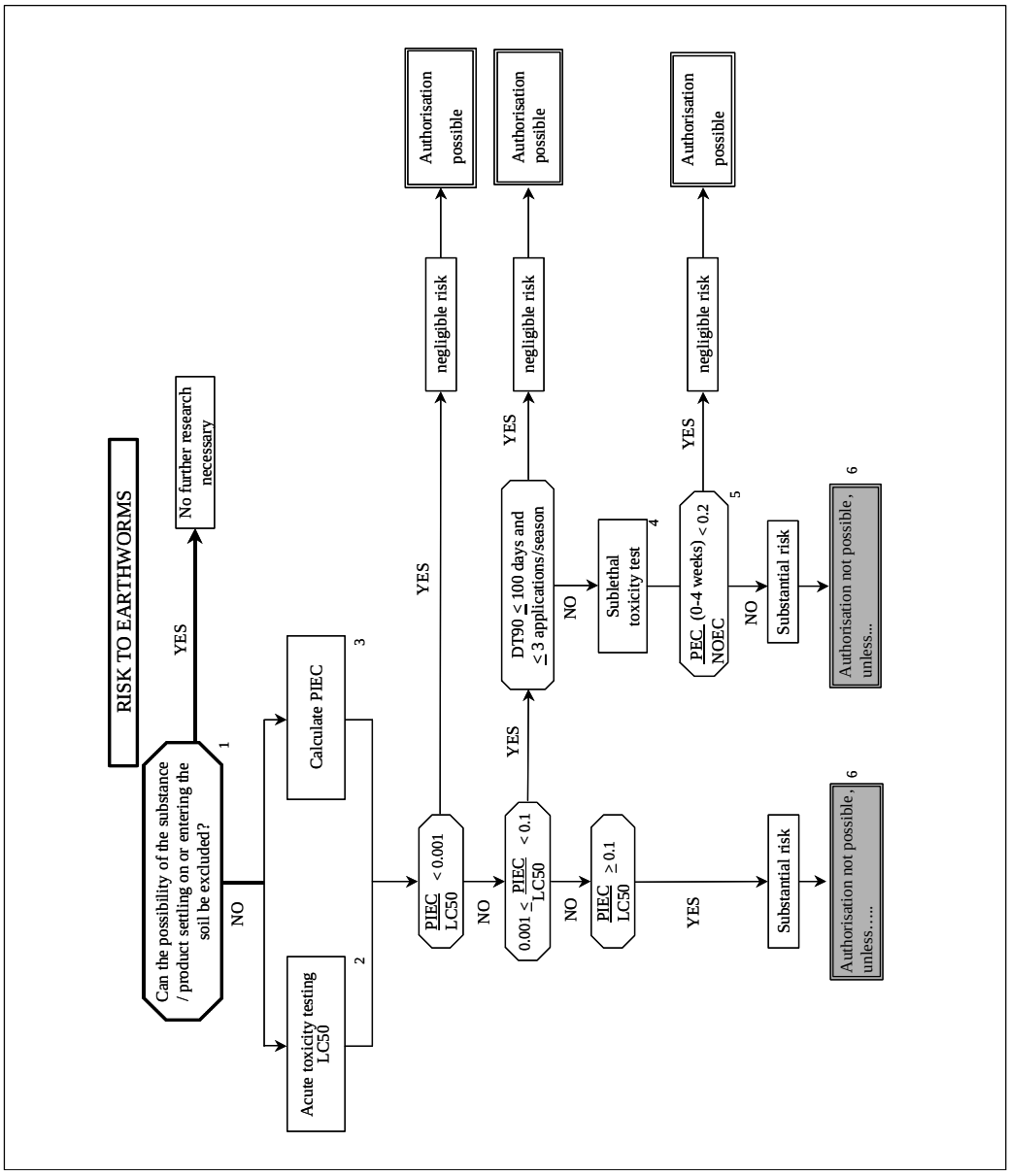

Figure 4 Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning the risk to eathworms (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

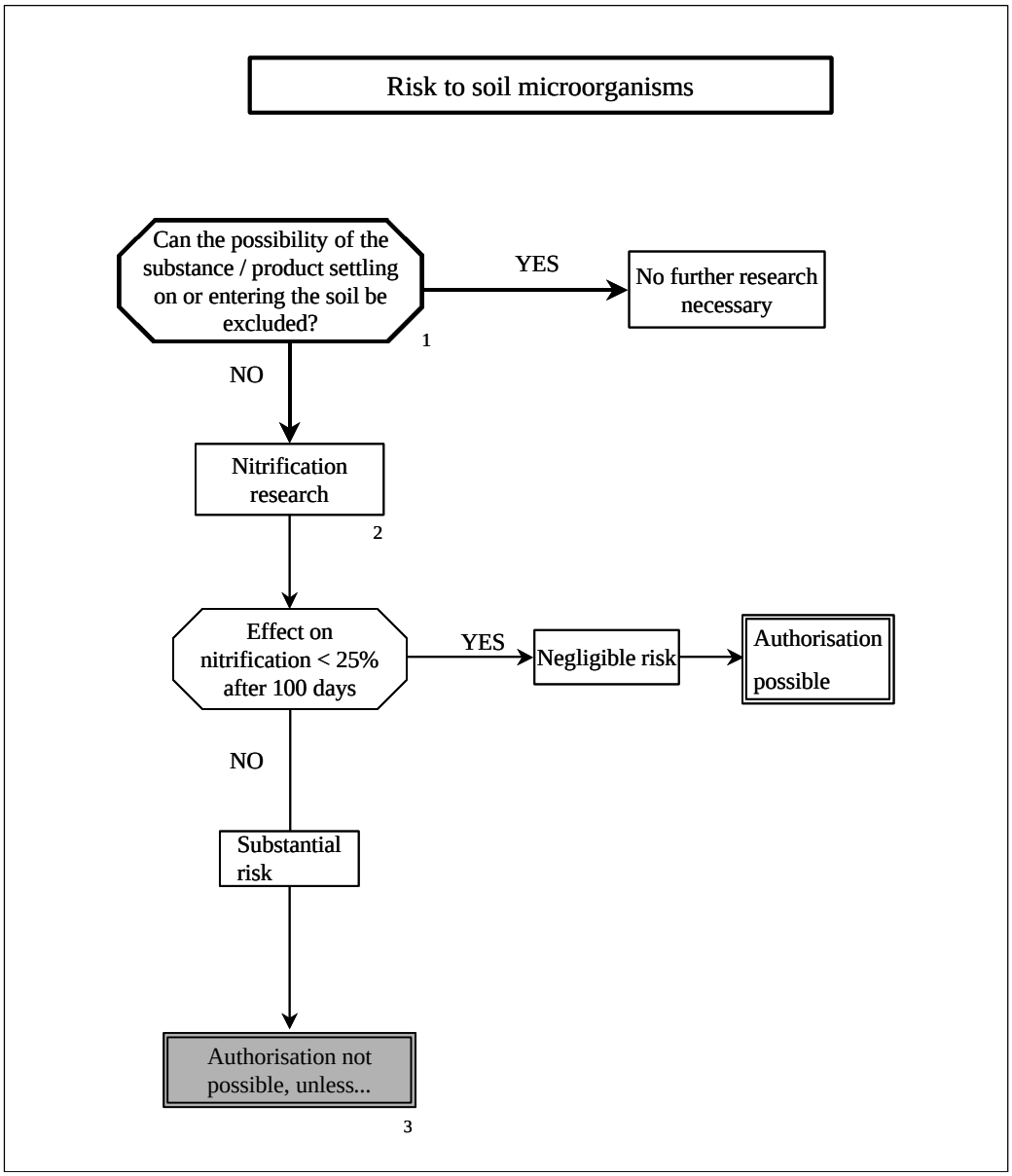

Figure 5 Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning the risk to microorganisms in the soil (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

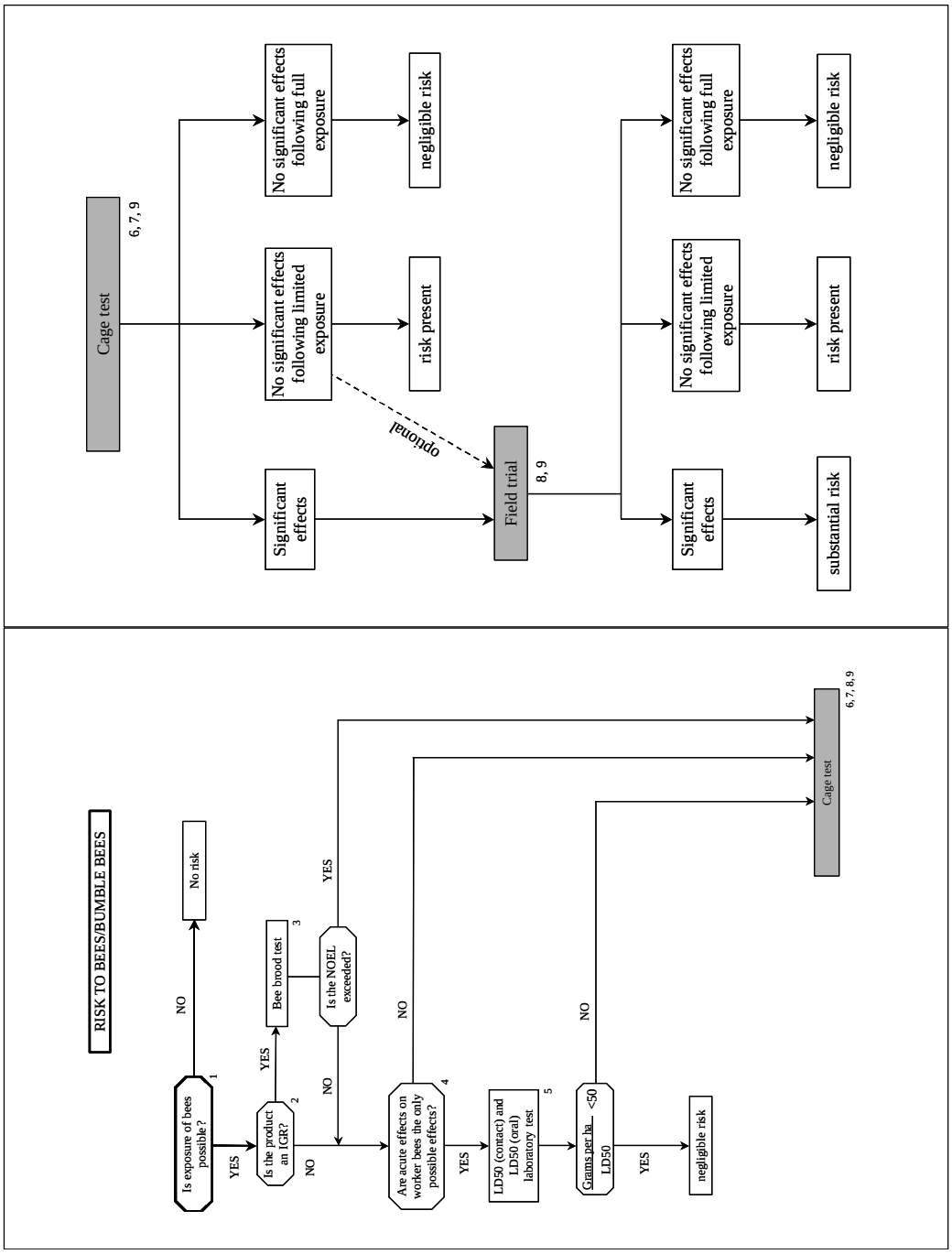

Figure 6 Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning the risk to bees and bumble bees (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

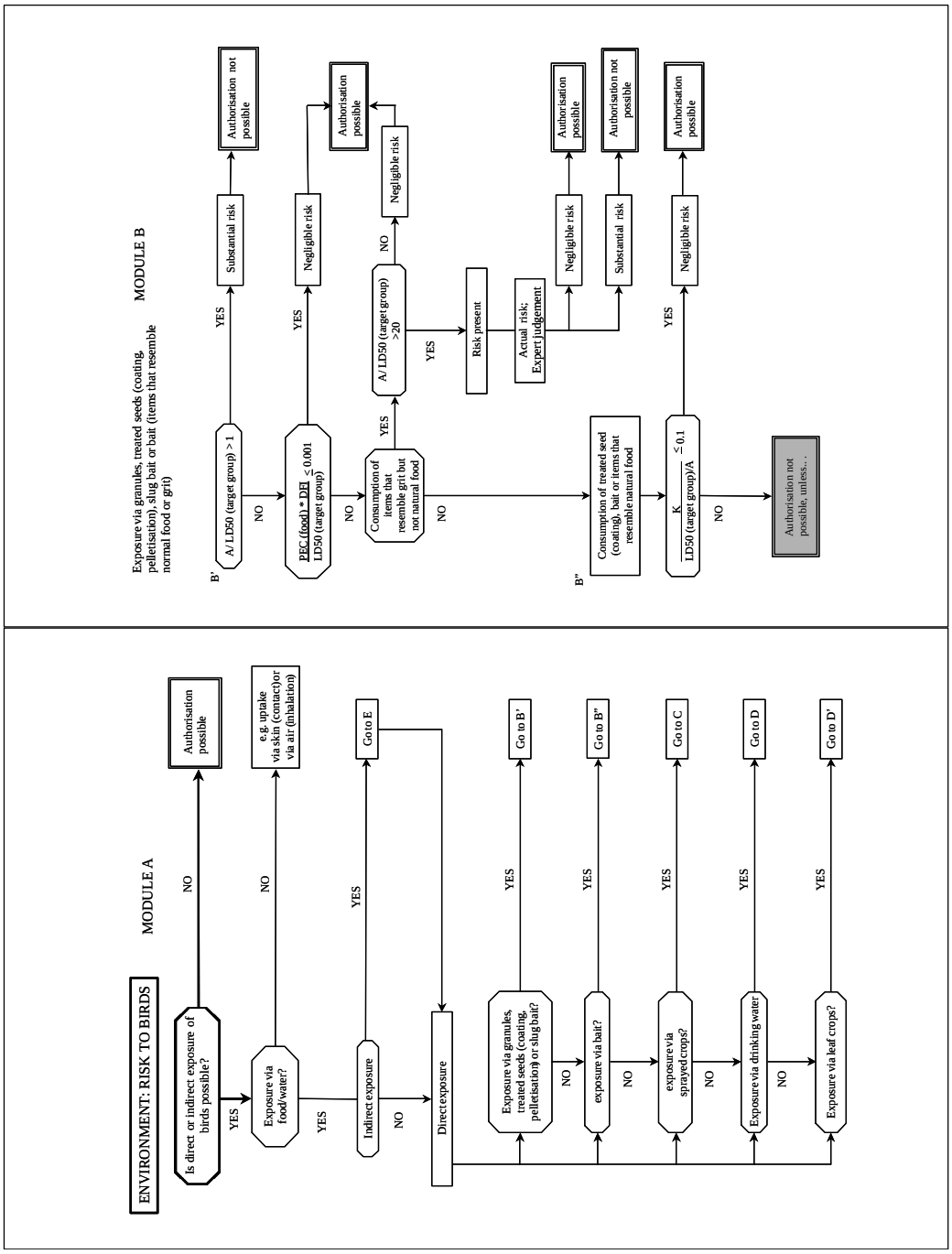

Figure 7 Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning the risk to birds (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

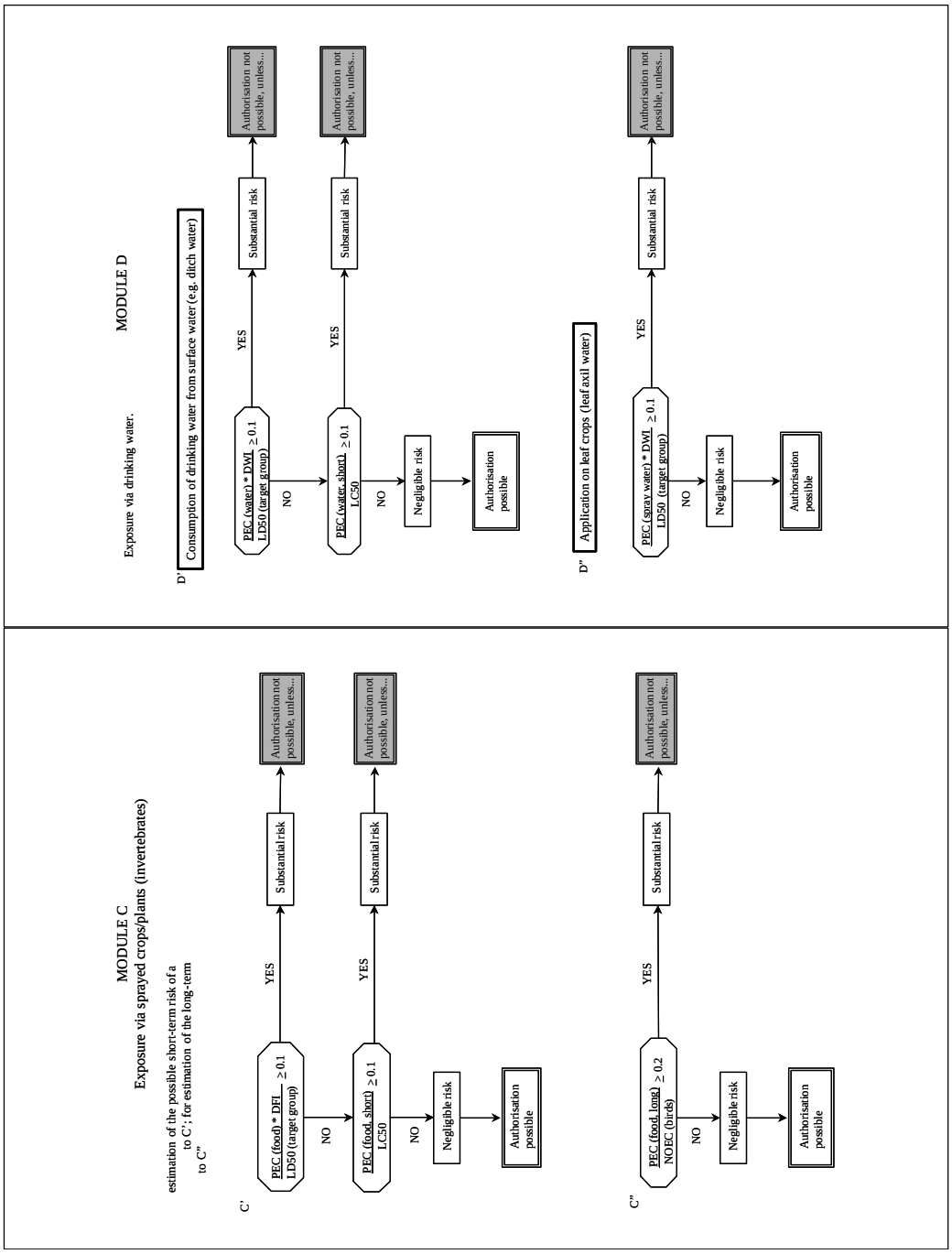

Figure 7 continued Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning the risk to birds (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

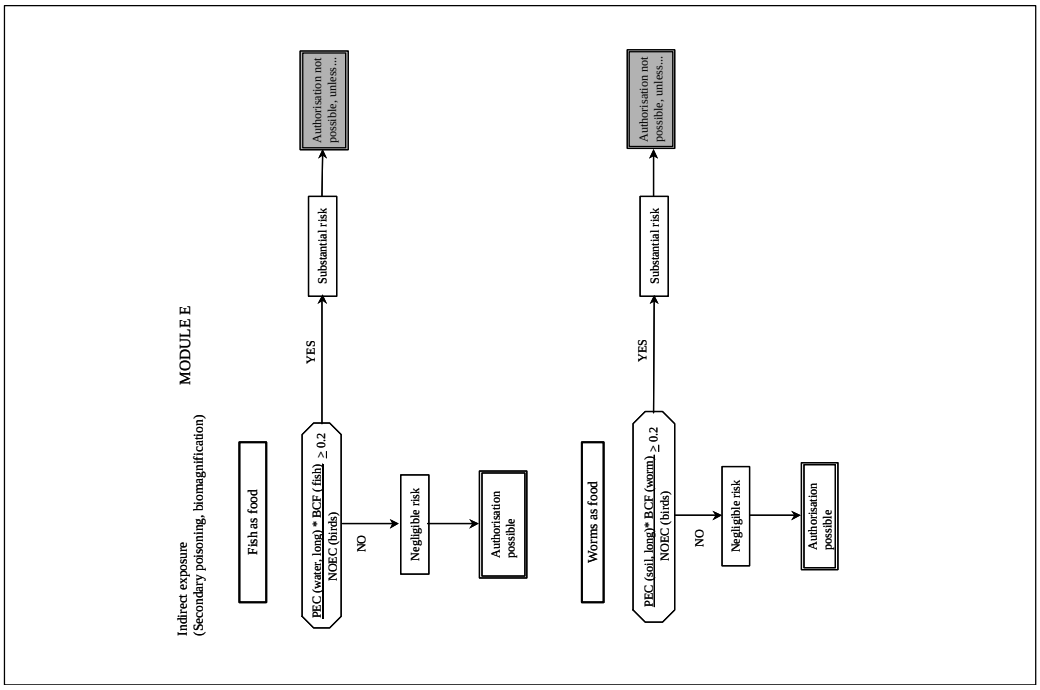

Figure 7 continued Decision-making scheme used by the CTB to test a plant protection product against the environmental requirement concerning the risk to birds (CTB99). The shading indicates where data from field research can be used for decision-support purposes.

Annex **E**

Forms of supplementary pre-registration (field) research

A survey of the various forms of supplementary pre-registration (field) research that can be conducted for the second tier of the risk assessment procedure is presented below. The survey is intended to give an impression range of possibilities; it is not intended to be exhaustive.

environmental criterion	*type of (field) research*
persistence in soil	field experiment or lysimeter experiment to determine the rate of conversion; lysimeter experiments possibly involving radioactively labelled substances
	lysimeter experiment to determine the percentage of soil-bound residues
	field experiment or lysimeter experiment to determine the concentration in the soil two years after the final application
	single-species laboratory tests involving non-standard test species for probabilistic risk assessment
leaching into ground water	lysimeter studies, possibly involving radioactively labelled substances
	field experiment involving ground water sampling
risk to aquatic organisms	single-species laboratory tests involving non-standard test species for probabilistic risk assessment
	single-species laboratory tests involving realistic exposure, for example, as a result of the addition of sediment
	single-species laboratory tests involving simultaneous presence of

environmental criterion	*type of (field) research*
risk to aquatic organisms (continued	simple multi-species laboratory tests involving a small number of species
	simple (generic) microcosmic laboratory studies involving more species from various trophic levels; high degree of standardisation; known species composition
	semi-realistic microcosmic laboratory studies; community taken from the field; controllable climatic conditions
	semi-realistic microcosmic and mesocosmic studies in the open air; same as the last category, but normally larger and allowing for interaction with natural environment (variable climatic conditions, import and export of organisms)
risk to earthworms	field test in the open air
risk to bees and bumble bees	bee brood test for the study of growth regulators
	cage and tunnel tests in the open air to study exposure, toxicity or organism behaviour
	field tests in the open air; same as the last category, but on a larger scale, without restriction of animal's freedom of movement
risk to birds	field test in the open air
risk to beneficial arthropods	research into persistence and biological availability on foliage under field conditions
	single-species laboratory test involving realistic exposure by means of natural substrate addition (vegetable material or soil)
	single-species cage test in the field, using organisms reared in the laboratory
	open-air field test involving one or more naturally occurring or introduced organisms reared in the laboratory