

**Mitteilungen aus der Biologischen Bundesanstalt  
für Land- und Forstwirtschaft  
Berlin-Dahlem**



**Criteria for assessment of plant  
protection products in the  
registration procedure**

by

**Abteilung für Pflanzenschutzmittel  
und Anwendungstechnik**

Biologische Bundesanstalt für Land- und Forstwirtschaft,  
Braunschweig

Heft 285

Berlin 1993

*Herausgegeben  
von der Biologischen Bundesanstalt für Land- und Forstwirtschaft  
Berlin-Dahlem*

Kommissionsverlag Paul Parey, Berlin und Hamburg  
Seelbuschring 9-17, D-1000 Berlin 42

ISSN 0067-5849

ISBN 3-489-28500-X

Die Deutsche Bibliothek – CIP-Einheitsaufnahme

Criteria for assessment of plant protection products in the registration procedure / by Abteilung für Pflanzenschutzmittel und Anwendungstechnik, Biologische Bundesanstalt für Land- und Forstwirtschaft, Braunschweig. Hrsg. von der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem. – Berlin; Hamburg : Parey [in Komm.], 1993

(Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft Berlin-Dahlem; H. 285)

ISBN 3-489-28500-X

NE: Biologische Bundesanstalt für Land- und Forstwirtschaft < Berlin; Braunschweig > / Abteilung für Pflanzenschutzmittel und Anwendungstechnik; Biologische Bundesanstalt für Land- und Forstwirtschaft < Berlin; Braunschweig > : Mitteilungen aus der ...

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1993 Kommissionsverlag Paul Parey, Berlin und Hamburg, Seelbuschring 9-17, D-1000 Berlin 42  
Printed in Germany by Arno Brynda, 1000 Berlin 62

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## **Preface**

In the framework of the authorization of plant protection products the applicant has to submit extensive documents to the Federal Biological Research Centre for Agriculture and Forestry (Biologische Bundesanstalt = BBA) for evaluation. The present booklet shows which criteria and within which framework the documents submitted for the various test areas are evaluated in the authorization procedure by the BBA.

The present issue is a translation of the booklet of the series "Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem" Vol. 284, 1992. During the course of the translation work further discussions led to some differences to the original German text in some chapters.

It becomes clear from the individual chapters that, as a rule, the decision-making cannot be reduced to keeping fixed limits, but, in many cases values are discussed which are a basis of the overall evaluation of a plant protection product in the framework of a risk-benefit analysis. However, in certain cases, based on the evaluation results of single test areas an authorization can be refused by so-called cut-off criteria.

The authorization procedure involves not only the BBA, but their decisions with regard to human health and animal health are made in agreement with the Federal Health Office (Bundesgesundheitsamt = BGA) and concerning the prevention of damage as a result of water and air pollution and waste disposal in agreement with the Federal Environmental Office (Umweltbundesamt = UBA).

The BGA too publishes in this booklet its assessment criteria of plant protection products in the authorization procedure. the assessment procedure of the UBA was taken into account in the respective chapters, as far as possible, by the authors of the BBA so that the present text is widely agreed by the involved partners.

I would like to thank the authors of the individual chapters

as well as the members of the editorial committee who ensured, as far as possible, a uniform structure of the chapters and who introduced certain comments of the institutes of the Federal Biological Research Centre for Agriculture and Forestry (BBA): Dr. Frost, Dr. Heimbach, Dr. Hommes, Dr. Joermann, Dipl.-Biol. Köpp, Dr. Nolting, and Dr. Wilkening. Further thanks are due to Mrs. Siadat for typing the manuscript.

An important purpose of this brochure is to make the evaluations in the authorization procedure transparent and to make them available to the public for discussion.

Braunschweig  
December 1992

A handwritten signature in black ink, appearing to read 'F. Klingauf', with a stylized flourish at the end.

Professor Dr. Fred Klingauf  
President of the Federal Biological Research  
Centre for Agriculture and Forestry

## Introduction

According to Article 15 of the Plant Protection Act the BBA grants an applicant authorization if the application fulfils the requirements set out in Article 12 and an examination of the plant protection product shows that

1. the plant protection product is sufficiently effective in the light of scientific knowledge and technique
2. the precautions necessary for the protection of human and animal health in dealings with dangerous materials do not require otherwise, and
3. the plant protection product, when used for its intended purpose and in the correct manner, or as a result of such use,
  - a) does not have any harmful effects on human and animal health or on ground water and
  - b) does not have any other effects, particularly with regard to the natural balance, which are not justifiable in the light of the present state of scientific knowledge.

The application must contain the data and samples required for proving the authorization preconditions. The requirements are specified by the Regulation on Plant Protection Products of 28 July 1987 and are described in detail in numerous national guidelines of the BBA and, in part, also in international guidelines.

The BBA as well as the BGA and the UBA being authorities of consent for the authorization have often been asked about which criteria according to which the authorization documents are evaluated and how, for example, decisions on denial of authorizations come about.

Such information is particularly important for applicants, since in advance of the authorization they are able to estimate to what

extent their respective products have a chance to be authorized after examination in the evaluation procedure. Also the public has a right to know that the decisions of the authorities are being transparent.

In this booklet the current evaluation principles of the BBA for examining plant protection products within the framework of the authorization procedure are described in chapters 1 - 17. The procedure of the BGA within the framework of the examination of toxicology is presented in Chapter 18. In the assessment concerning fate in water, air, waste disposal, and effects on water organism the attempt has been made to take into consideration as far as possible the procedures of the UBA (see UBA-Principles on criteria and procedures for environmental assessment of pesticides, Chemosphere, 24/6, p. 793-815, 1992). It should be noted, however, that the evaluation criteria are continuously being revised and adapted to the current status of information, e. g. further discussions resulted in some differences to the original German text.

This framework of evaluation has been considered in the draft versions of the annex VI, "Uniform Principles of the Evaluation of Plant Protection Products" provided for the "Council Directive of 15 July 1991, Concerning the Placing of Plant Protection Products on the Market" of the EC, to be achieved by the twelve EC-members. After adoption of the "Uniform Principles" by the Council of the EC the evaluations on hand, in single cases, have to be adapted to the EC-regulations.

The attempt has been made to structure the individual chapters according to a scheme as uniform as possible. After a short description of the subject a listing of the respective relevant guidelines is given, according to which the trial results should be worked out. Where possible, it is also presented when products and claimed uses, respectively, can be excluded from corresponding examinations.

Furthermore, the chapters contain as much as possible  
- a listing of when on the basis of the data situation an assess-



- ment is not possible;
- the presentation of the decision-making produced from the submitted data;
- flow diagrams for clear presentation of the decision-making.

As a rule, the evaluations are to be seen in connection with the guidelines of the BBA. These guidelines are available from "Saphir Verlag Heike Kramer, Gutsstraße 15, D-3171 Ribbesbüttel". A corresponding list of publications of the BBA with respect to evaluation, authorization, and application of plant protection products can be requested there as well.

**The here presented evaluation-framework does not replace the commentary for instructions to fill in the BBA-application form AP 01-05 given in the BBA-guideline part I, 1-2.**

The following decisions are possible in the various test areas:

- authorization without restriction;
- authorization with placing of labelling requirements;
- individual claimed uses are not provided for authorization;
- decision on authorization dependent on risk-benefit analysis;
- no authorization of the product (cut-off criteria).

In the analysis of the risk-benefit and decision-making on what is to be understood as other effects in particular on the natural balance, which are not justifiable in the light of the present state of scientific knowledge, reference is made to the so-called "Paraquat decision" by the Federal Administrative Court of 10 November 1988. Concerning these questions the Federal Administrative Court has set up the following principles:

- "Other effects" ("side effects") in the meaning of article 15, para. 1, no. 3, letter b of the Plant Protection Act (1986) are all effects that cannot be precluded with probability bordering in certainty.
- For the decision whether the other effects of a product are "not scientifically acceptable", the probability of the occurrence of the effects, the weight of the disadvantages of the effects, the

replacability of the product and the disadvantages of not using the product are to be weighed against one another.

- In the decision on the scientific unacceptability of the other effects, the authority is not entitled to any latitude in assessment.

K. Claussen, W. Dobrat, G. Menschel

### **1. Chemical and physical properties, composition**

For the authorization of a plant protection product the applicant has to submit data on

1. chemical and physical properties of the product and of the active ingredients; non-active ingredients and impurities contained therein, as well as the decomposition and reaction products, and
2. methods of analysis to determine the active ingredients and, if appropriate, the non-active ingredients and impurities in the formulated product.

The data, studies and procedures required are described in detail in the BBA Guideline I, 1-2. All data and documents must be complete, assessable and plausible. If appropriate, the BBA will carry out experiments to verify them.

### **Assessment**

#### **Negative assessment of the test area**

#### **No authorization of the plant protection product (cut-off criteria):**

- The required methods of analysis were not submitted, or the methods submitted are obviously not suitable for the formulation in question.
- In the experimental testing the analytic method proved to be unsuitable (since, for example, no or only insufficient separation of other active ingredient(s), impurities of active ingredient(s), non-active ingredients, etc. can be achieved, the active ingredient content cannot be determined).
- The chemical composition of the product does not agree with that reported in the application form (range of tolerances for active ingredient contents: according to FAO specification or "Manual on the development and use of FAO specifications for plant protection products").

- The product contains
  - hazardous non-active ingredients (carcinogenic substances of groups A 1, A 2 and B and/or teratogenic substances of groups A and B according to Technische Regeln für Gefahrstoffe (TRGS 900)).
  - in toxicologically relevant concentrations substances that, on the basis of the Gefahrstoffverordnung or other regulations, may not be marketed.
- The impurities of the active ingredient(s) exceed the limits established in the FAO specifications, the BBA guideline I, 3-4, and/or the new version of the EC Guideline 79/117/EEC.
- Lack of physical properties (insufficient suspensibility or emulsion stability etc., e. g. according to CIPAC as contained in FAO specifications) cannot be corrected by slight reformulation (minor change), rather the product must be reformulated on a larger scale, so that new tests of efficacy, residue, and/or environmental behaviour become necessary.
- The product cannot be handled/applied/stored. The basis for the evaluation are physical properties of the product, the scope of which is described, e. g. corresponding to the FAO specifications (guidelines) for the individual formulation types. To the extent that these specifications contain recommendations for certain parameters (such as storage temperature 54 °C or 0 °C) or recommendations for limits, these can be used for evaluating the product. Deviations are not automatically exclusion criteria, rather the applicant is requested to submit statements. The product should be rejected only if in the physical-chemical or technical application properties distinct deviations from these guidelines or international quality standards occur.
- Despite suitable protective measures the user is endangered by the product, e. g. by an intolerably high dust formation or the like.

K. Claussen

## **2. Waste disposal**

As waste particularly in need of monitoring, plant protection products that can or may no longer be used are to be disposed of in a way that poses no threat to humans or the environment.

Reference is made in BBA Guideline I, 1-2, to the tests necessary with regard to waste disposal.

Comprehensive studies of the combustibility of plant protection products for the purpose of disposal have shown that plant protection product wastes can be incinerated in household trash incinerator plants without significantly increasing the emission of chlorinated dibenzodioxins and -furans - expressed in toxicity equivalents.

On the basis of results available, further tests with active ingredients currently on the market do not appear to be necessary. In the case of new active ingredients with a halogen content of more than 60 % (guideline level now being discussed), studies of combustion behaviour are to be worked out as required. A corresponding guideline is in preparation.

Details on the actual disposal method for the separately collected plant protection product wastes that are then to be incinerated in the household trash incineration plants are still to be arranged among the participating federal authorities, the competent offices of the states and the operators of the household trash incineration plants (UWSF-Z. Umweltchem. Ökotox. 4(3) 1992, p. 136-145).

Only in the case of a few products an incineration along with household trash will not be possible. It is planned to get rid of these products in special incineration plants or to store them in pit dumps. The dump method of disposal should be precluded in the future in view of the generating new waste burdens.

M. Blacha-Puller, J. Siebers

### **3. Residue analysis**

Monitoring methods and test report methods are required from the applicant.

#### **3.1 Monitoring methods**

The analytical methods submitted in the authorization procedure are to be available to the official food control, the water, environment and health administration as well as the concerned industries for determination of the residues of plant protection products, including relevant metabolites, in soil, water, food, feed and processed products.

A position is to be taken on the applicability of the multimethods S 8 and S 19 of the "Manual of Pesticide Residue Analysis, Vol. I" of the Deutsche Forschungsgemeinschaft (VCH-Verlagsgesellschaft, Weinheim) used predominantly in food monitoring and cited in the "Official Collection of Test Methods According to § 35 LMBG (Amtliche Sammlung von Untersuchungsverfahren nach § 35 LMBG)." The results of the validation are to be submitted for the most important crops. If it is apparent from the properties of the active ingredient/metabolites that the multimethods cited are not applicable, a brief justification suffices. In these cases another multimethod or single method is to be submitted. Excepted from these requirements are substances such as grafting waxes, carbon dioxide, nitrogen, rape seed oil, several game gnawing products.

Effective January 1st 1993 methods for the direct determination of plant protection products in the air are also required.

The required data are explained in BBA Guideline I, 1-2 (November 1990, pages 20-22).

#### **3.2 Test report methods**

To be submitted are those analytical methods that are used to produce test reports on degradation in the soil, leaching behaviour, on residue behaviour in crops and processed products,

as well as for animal materials and for testing the volatility behaviour. These methods are assessed together with the test reports in the respective schemes.

### **3.3 Data required**

The following documents or data are absolutely required for evaluation of the analytical methods:

- detailed, reproducible, quotable working instructions;
- limit of determination and limit of detection; the limit of determination must be validated by recovery experiments;
- recovery rates and variation of the recovery rate;
- blank values,
- typical chromatograms.

### **Assessment**

The methods submitted will be evaluated according to the following principles. In certain cases the methods are tested experimentally by the BBA. A negative decision in this scheme will occur in the following cases:

- limit of determination for active ingredient and/or metabolites not adequate for checking the maximum residue limits or the drinking water regulations. For soil, a determination limit of  $\leq 0,05$  mg/kg is required.
- Mean recovery rates outside of 70 - 110 %, except in special, justified cases.
- Relative standard deviation of the recovery rates  $> 20$  %, except in special, justified cases. (The overall relative standard deviation and the relative standard deviation for each fortification level is to be indicated separately for each test material.)
- Method too non-specific. Blank values as a result of interfering substances frequently  $> 30$  % of the limit of determination.
- Unacceptable experimental or apparatus expenditure in methods for monitoring purposes.
- Method not reproducible in experimental testing.

With negative decision in this scheme an authorization certificate for the product will as a rule not be granted (cut-off criterion).

E. Bode, G. Heidler, J. Martin

with collaboration by:

K.-H. Berendes, H. Ehle, H. T. Laermann, U. Meier

#### **4. Efficacy and crop tolerance (phytotoxicity)**

An essential purpose of the Plant Protection Act is to protect crops and plant products against harmful organisms and non-parasitic impairments (Art. 1 nos. 1-2 Plant Protection Act). In addition to other measures, the application of effective plant protection products in particular contributes to realizing the goal of this Act.

The BBA has published a large number of guidelines that serve the experimenter as instructions in the testing of plant protection products for efficacy and crop tolerance within the framework of the authorization process (Guidelines for the Testing of Plant Protection Products, Part II - Efficacy). If in the individual case no guideline exists, the tests are to be designed and evaluated based as far as possible on the guidelines for similar testing projects.

##### **4.1 Data requirements**

To demonstrate the authorization prerequisites in the sub-schemes "efficacy" and "crop tolerance" (phytotoxicity) it is necessary for every claimed use listed in the application form for authorization to submit test reports that permit an evaluation of the efficacy (Art. 12, para. 3, sentence 2 of the Plant Protection Act in conjunction with Art. 15, para. 1, no. 1 Plant Protection Act and Art. 1, para. 2, no. 2 letter a, of the Regulatory Ordinance on Plant Protection Products and Plant Protection Equipment). It is also to be tested whether the use of the product causes damage to the plants to be protected or quality impairment to crops or processed products. Any damage or deterioration occurring are to be described by nature and extent.

In the testing of a product for sufficient efficacy the greatest possible spectrum of variable influencing factors is to be encompassed.



Details are found in the section of the "Guideline for the Testing of Plant Protection Products in the Authorization Process, Part II Efficacy, 1 General and Part I General on the Procedure for Testing and Authorization, 1-2 Application for First/Renewed Authorization of a Plant Protection Product, Instructions for Completion."

#### **4.2 Course of testing**

The course of testing is shown in diagram 4a for assessing the "Efficacy" and "Crop Tolerance" (Phytotoxicity) for a claimed use of a plant protection product.

##### **4.2.1 Harmful organism - protective purpose**

The claimed use is first to be examined to determine whether the harmful organisms cited in the application form for authorization involve organisms according to Art. 2, para. 1, no. 7 of the Plant Protection Act which in one or all development stages cause unacceptable damage or quality reduction to plants or plant products, sharply hinder the harvesting of a crop or present a hazard. In other cases, e. g. with growth regulators, sprouting inhibitors or animal repellents, it is to be examined whether through non-use of a product considerable (economically unacceptable) damage, including quality losses, actually occur.

It is of no significance here whether the damage is caused regularly. Exclusively decisive is the scientific fact, or the fact founded on experience, that considerable damage can be caused.

##### **4.2.2 Usability and ability to handle the product**

The description given in the application form regarding the time of application of the product and the crop, or regarding the protective purpose is first examined for its plausibility. In the second step the wording intended by the applicant on the claimed use is compared in the point cited for agreement with the corresponding data of the test reports on efficacy. Any discrepancies are to be clarified in a dialogue with the applicant.

The practical test of efficacy yields indications on the ability to handle the product (e. g. foam formation, blockage of nozzles, flowability of powder formulations) that can lead to a detailed testing in the authorization process.

#### **4.2.3 Choice of dosage (fixing the minimum effective dosage)**

It is to be founded in the application form for authorization that the intended dosage of a product has been selected as low as necessary for achieving adequate efficacy (minimum effective dosage, see Guideline for the Testing of Plant Protection Products, Part I, 1-2).

#### **4.2.4 Efficacy**

Foreword

One of the most important authorization prerequisites in the prove of sufficient efficacy according to the state of scientific knowledge and technology. The indefinite term "sufficient efficacy" indicates that with a test product when used as intended (application according to the purpose obvious from the instructions for use) and with proper application (corresponding to good agricultural practice) it is possible to achieve an efficacy that meets the average requirements of the practice or that is comparable to the reference product. The level of these requirements depends on various factors. These include, for example, the state of plant protection product development and equipment technology, the biological properties of the harmful organism to be controlled or repelled, taking into consideration the influence of antagonistic species, the significance of the protective purpose to be met (sprouting inhibition, repelling birds, etc.) and the demands on the quality of the crops or harvest to be protected.

The studies on the efficacy of a product are to be conducted in various regions of the Federal Republic of Germany or also at comparable locations in neighbouring countries and, as a rule, during two test periods. This procedure checks on whether the sufficient efficacy can also be achieved in unfavourable conditions in practice (e. g. with regard to infestation pressure, infestation severity, soil conditions, weather conditions or

development stage of the harmful organism).

#### **4.2.4.1 Frequency and technique of application**

Closely connected to the determination and evaluation of sufficient efficacy are application technique and application frequency. Without suitable application technique the required efficacy is to be achieved, if at all, only with increased product dosages. Negative effects of the application technique can be derived indirectly from the test reports on efficacy of a plant protection product.

The number of product applications necessary to achieve sufficient efficacy is different depending on the harmful organism or protective purpose and mode of action of the product. If the number is not of necessity found from the claimed use (e. g. "seed treatment products" or "application at sowing" to be used only once), establishment of the maximum application frequency lies with the applicant. The necessity of more than one application is always to be indicated whenever in order to achieve its purpose a product must be available in an effective dose continuously over a lengthy period of time. This is true especially for most fungicides, but also for products against virus vectors in potatoes, for rodenticides (anti-coagulants must be applied several times and taken up; in the case of commensal harmful rodents elimination of the infestation is considered the goal of control) or, e. g., for biological and biotechnical plant protection products with a short duration of efficacy.

#### **4.2.4.2 Sufficient efficacy (degree of efficacy)**

In only a few cases is an efficacy of 100 % or almost 100 % absolutely necessary or at least to be sought. These high requirements apply to fumigants in stock protection and with quarantine fumigation, in controlling commensal, disease-carrying harmful rodents, in some fungicidal seed treatment products and in applications to crops that, because of legal regulations or economic requirements, must satisfy high quality demands (e. g. seeds or plantings, ornamental plants, hops, raw tobacco).

In the remaining cases no degree of efficacy is established which

must at least be attained, but no efficacy is accepted that does not make it possible to control a harmful organism or achieve a protective purpose under unfavourable practical conditions. This strict criterion in product testing must be maintained, because ineffective or insufficiently effective products can cause severe economic losses and additionally unnecessarily stress the environment. Moreover, the amount of a product needed because of the efficacy requirements, if necessary including the possible number of applications during a vegetation period, forms the basis for a large number of tests in the authorization process, especially with regard to possible effects on the health of humans and animals, on the ground water and the environment. Thus, in addition to sufficient efficacy of the product even under difficult conditions, the user of a plant protection product authorized under the prerequisites cited can also with authorized and proper application assume that all legal requirements for the protection of the health of humans, animals, ground water and environment are being observed. Consequently, a user should not apply a higher amount of a product than provided for by the authorization and thus indicated in the instructions for use. Applicant and authorization authority would, however, be confronted by an insoluble problem to establish within the framework of the authorization process the amount of a product needed under certain more favourable conditions. These necessary decisions, e. g. reduction of the amount of a product provided for in the authorization, must be made on the spot by the advice service and the user himself with knowledge of the respective facts of the matter (e. g. resistant varieties, low infestation pressure).

Similarly manifold influencing factors which cannot be appropriately covered in the authorization process determine the economic damage threshold, the level of which depends not least of all on the economic conditions of the producer concerned. Aside from the fact that today there are quite few reliable economic damage thresholds, their necessarily great variability does not offer any reliable basis for the evaluation of the sufficient efficacy of a product.

In addition to the evaluation of the efficacy, yield response accompanying the reduction of harmful organisms is an index of the efficacy of the test product. If yield assessments are viewed as necessary, it can be seen from the respective guidelines for testing plant protection products in the area "efficacy."

#### **4.2.5 Plant tolerance and quality of the harvested crop**

During the investigations on the efficacy of a plant protection product special attention is given to the observation of possible damage to crops ("phytotoxicity") as a consequence of applications of the product. In special cases, e. g. for testing the germination ability of treated seed or for detecting quality deteriorations in crops and stocks or special processed plant products, special tests become necessary (e. g. off-flavour and taste tests for strawberries, fermentation and taste tests for wine). In case of doubt, or if no test guidelines are available, the tester should contact the BBA.

The use of a plant protection product should in no case cause plant damage, quality deteriorations or other negative effects (e. g. for hay bales, planting substrate). Should such effects occasionally occur, it must be examined to what extent they are acceptable or to be avoided by observing the restrictions in this regard issued in the authorization certificate.

#### **4.2.6 Subsequent crops**

Data on the mode of action of the product or of the active ingredient are also to be submitted with the application form for authorization. In addition, effects on subsequent crops are also studied. For estimating the risk of plant damage to subsequent crops data for the potential products are required as part of the authorization process. The documents on decomposition behaviour with regard to possible damage to subsequent crops both main and break crops, through uptake of the active ingredient and still-effective decomposition products from the soil are to be compiled (see also diagram 4b "Tolerance of Plant Protection Product in Subsequent Crops"). These plant protection products include especially herbicides

- for the active ingredient of which an average DT90 value of

> 120 days has been determined in decomposition tests in the soil under Central European field conditions, or  
- which in reference to sensitivity to various crop species exhibit a ratio of sensitivity of > 1 : 100 to one another.

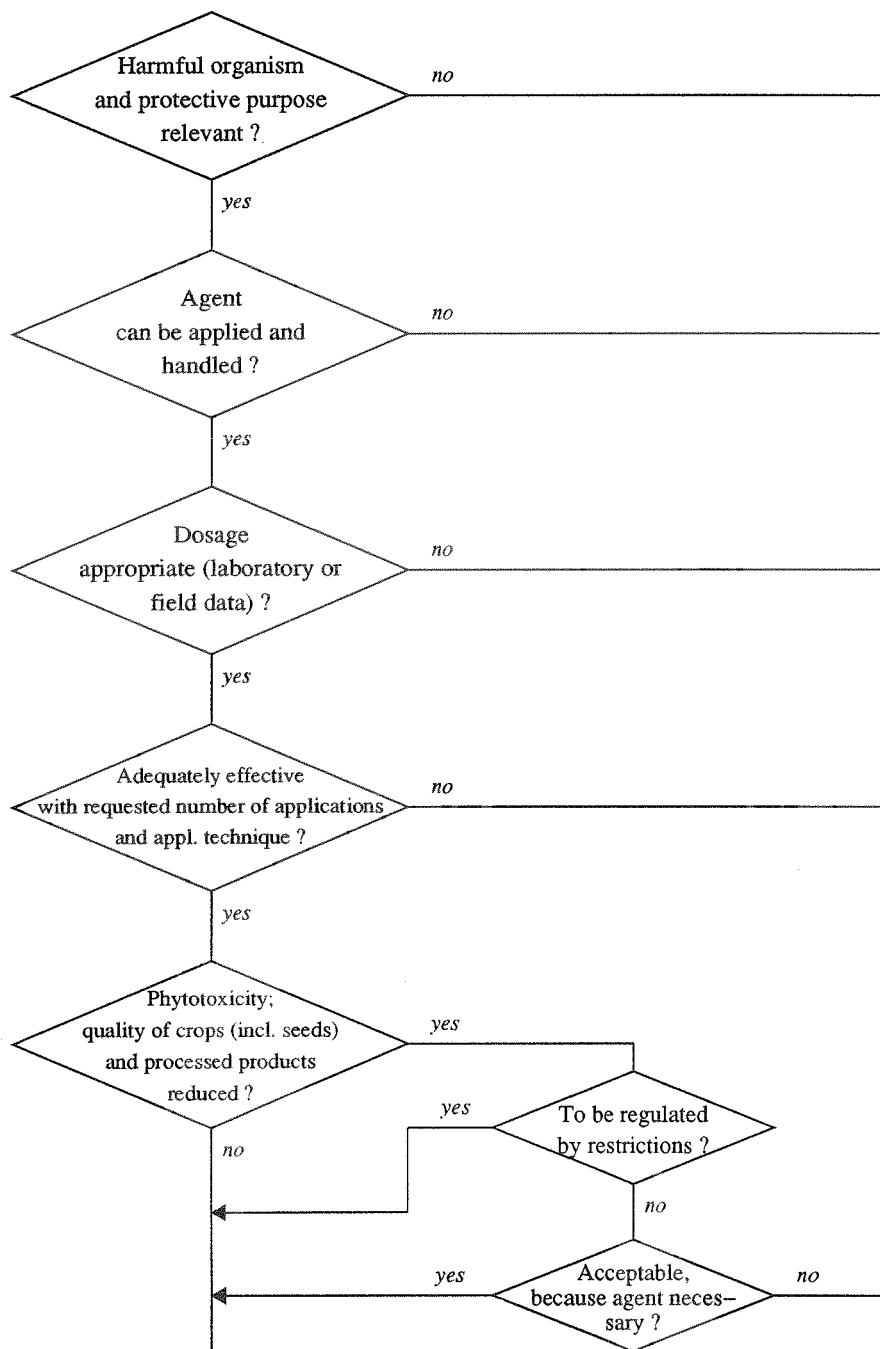
### Assessment

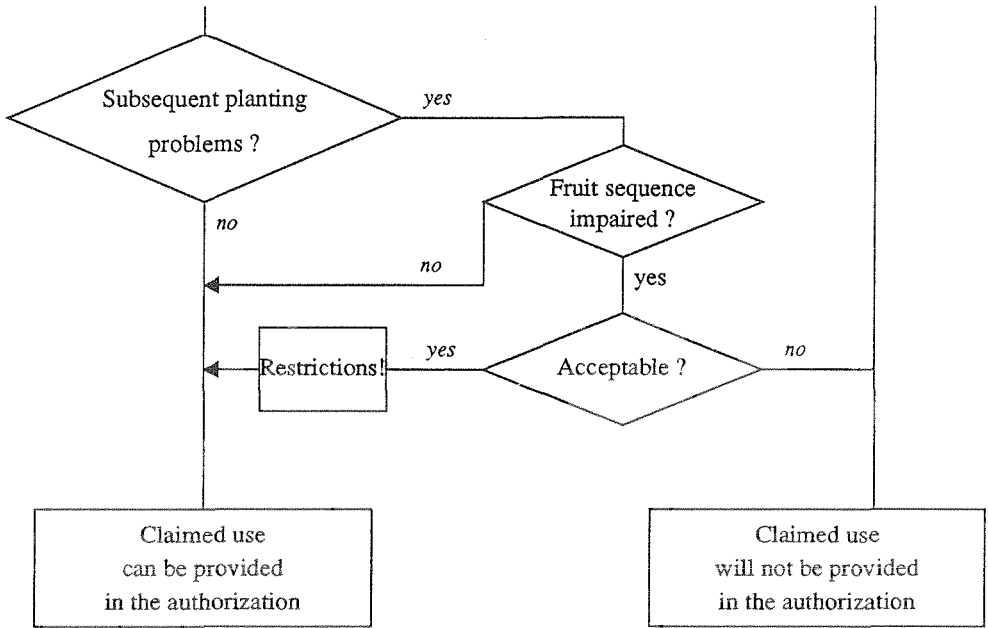
The decision paths in the scheme "Efficacy and Crop Tolerance" (Phytotoxicity) are shown in diagram 4a.

Only claimed uses in which a product is sufficiently effective are provided in the authorization. Ineffective products are not authorized since they unnecessarily stress the environment and cause the user superfluous costs for the product or through loss in yield. If the testing has shown that the product is indeed effective, but that damage occurs to crops that reduces the quality of the crop (including seed and processed products such as wine) or causes problems in subsequent crops, the claimed use cannot be provided in the authorization, or the product can be authorized only to the extent that these effects can be avoided in practice with observation of special precautionary measures. In addition, the authorization must always be in conjunction with restrictions of use if only thereby is proper application of the product possible. The instructions for use can then from the scheme "efficacy and crop tolerance" contain data and references, among others,

- regarding the number of applications ("When used against spider mites the application can be repeated several times at intervals of about 7 days if necessary"),
- regarding the spectrum of harmful organisms ("The product acts only against young, migrating larvae;" "positive-negative list for weed control"),
- regarding varietal tolerance ("Note varietal sensitivity for wheat"),
- regarding subsequent crops ("Under unfavourable climatic conditions damage to subsequent crops, especially winter cereals, is possible"),
- regarding occurrence of resistance ("Repeated use can lead to reduction in efficacy"),
- regarding application techniques ("Apply with suitable metering device and with uniform grain flow").

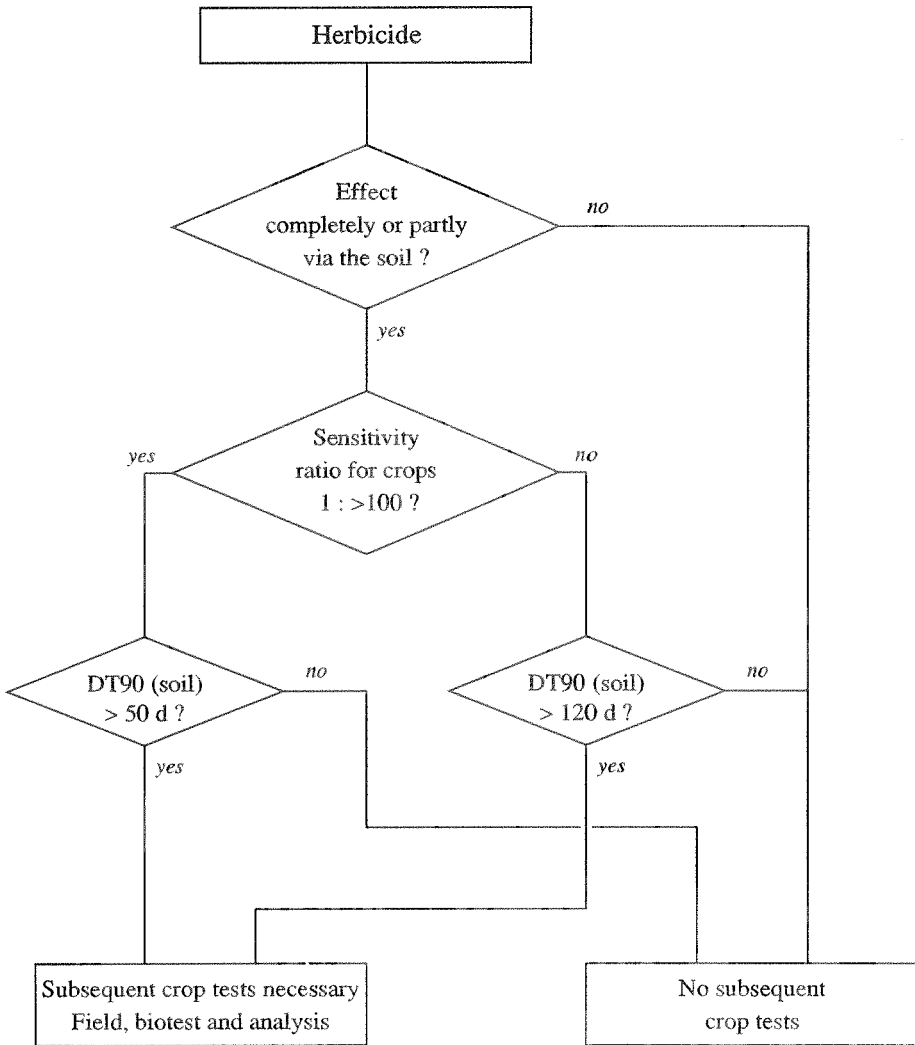
#### 4a. Efficacy and Crop Tolerance (Phytotoxicity)







4b. Tolerance of Plant Protection Products in Subsequent Crops  
(using the example of herbicides)



K. Hohgardt

## 5. Toxicology

### 5.1 Toxicological data for assessing the effects on humans and domestic animals; conclusions and toxicological limits

Information on the extent and execution of the necessary studies is given in the following guidelines:

- BBA Guideline Part I, 1-2, "Instructions for application for registration of a plant protection product"
- OECD Test Guideline for Testing of Chemicals, especially Section 4, Health Effects.

Many assessment principles have been published; some of these publications are cited below as examples.

- World Health Organization  
Principles for the Toxicological Assessment of Pesticide Residues in Food, Environmental Health Criteria 104, 1990
- Commission for Plant Protection Products, Plant Treatment Products and Stock Protection Products of the German Research Association
- Report VIII: Criteria for the toxicological assessment of plant protection products, plant treatment products and stock protection products (July 1974)
- Report XV: Criteria for the assessment of studies on genotoxicity with plant protection products (1985)
- Report XVII: Criteria for the assessment of studies on carcinogenicity with plant protection products (1990)
- Report XVIII: Criteria for the assessment of studies on reproduction toxicity with plant protection products (1990)
- Recommendations of the working group on toxicology: Toxicological studies in fish (1983)
- Procedural principles for determining safety factors for the health assessment of plant treatment products in:  
Data collection on the toxicology of herbicides, 4th installment 1983

The assessment principles of the Federal Health Office are specified in chapter 18.

## **5.2 User protection**

Information on the extent and execution of the necessary studies is given in the following guidelines:

- BBA Guideline Part I, 1-2, "Instructions for application for registration of a plant protection product"
- BBA Guideline Part I, 3-3, "Labelling of plant protection products - health protection - information on the instructions for use to protect the user, etc."
- BBA Guideline Part I, 3-3/1, "Labelling of plant protection products - health protection - risk assessment for the selection of suitable safety phrases and other measures for the protection of the user in the handling of plant protection products"
- BBA Guideline Part I, 3-3/2, "Labelling of plant protection products - health protection - description and suitability testing of the universal protective glove (plant protection), and the standard protective suit (plant protection)"

The assessment principles have been published:

- Commission for Plant Protection Products, Plant Treatment Products and Stock Protection Products of the German Research Association
- Report XIII: The assessment of health hazards for the user of plant protection products (1985)
- J.-R. Lundein, D. Westphal, H. Kieczka, B. Krebs, S. Löcher-Bolz, W. Maasfeld and E.-D. Pick  
Uniform principles for safeguarding the health of applicators of plant protection products (Uniform Principles for Operator Protection), Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, no. 277, 1992.

## **5.3 Labelling with regard to the regulations on hazardous materials**

The necessary documents and assessment principles are explained in the following guidelines and regulations:

- BBA Guideline Part I, 1-2, "Instructions for application for registration of a plant protection product"
- OECD Test Guidelines 401-405

- BBA Guideline Part I, 3-2, "Labelling according to the regulations on hazardous materials"
- Regulations on Hazardous Materials (Gefahrstoffverordnung-GefStoffV) of 6 August 1986, in the wording of the announcement of 25 September 1991

K. Hohgardt, U. Banasiak, H. Parnemann, W. Storzer

## **6. Residue behaviour**

### **6.1. General aspects**

The requirements on residue behaviour cited in the following sections apply in principle for every active ingredient/plant protection product. Depending on various factors, however, exceptions are possible at any time. Where these are clearly definable they are cited in the sections below. In particular cases it can nevertheless prove to be necessary to submit some data for information.

If the authorization is being called in question, a risk-benefit analysis has to follow. This analysis is done taking into consideration always the results of the toxicological tests.

**The authorization of a plant protection product or individual claimed uses is not possible in the following cases:**

- The use of an active ingredient that is contained in plant protection product foreseen in the authorisation procedure is restricted or completely forbidden in accordance with the Regulations on Plant Protection Application (Pflanzenschutz-Anwendungsverordnung).
- The active ingredient tends to accumulate in the food chain. This property is undesirable. Taking into consideration the results of other side-effects and the results of the toxicological studies it should lead thereto that the plant protection product or individual claimed uses cannot be authorized. The testing of the residue behaviour provides sufficient indications of enrichment factors for accumulation (see also items 6.6 and 6.7).

### **6.2 Uptake, distribution and mode of action in view of the residue behaviour in and on the plant**

The data on uptake, distribution and mode of action as a rule form an essential basis for assessing the residue situation. These documents are normally worked out in laboratory tests by means of radioactive labelled active ingredients.

Special guidelines on examining uptake, distribution and mode of

action do not exist at present. Indications of the nature and content of the necessary documents are given in the following guidelines:

- BBA Guideline Part IV, 3-1, "Testing of residue behaviour - General information on nature and extent of the required studies/documents -"

These studies are required for each active ingredient. Exceptions are, for example, nitrogen, carbon dioxide, sulfur, game-repellents, products for wound-sealing and grafting.

There can be no assessment if corresponding test reports are not available.

The information on uptake, distribution and mode of action are assessed neither positively nor negatively at this point. Examination of the information however has effects on other aspects of this scheme (nature and extent of the required residue trials, rotational crops). Use restrictions are not issued.

### **6.3 Breakdown, transformation, and metabolism in and on the plant**

The concept provides for a stepwise procedure beginning with a suspension cell culture test and ending with field/model tests on entire plants (a corresponding guideline is in preparation). The suspension cell culture test is required for every organic active ingredient. Studies going beyond this are required only for active ingredients used with plants or plant products used as food for humans and/or feed for animals. As in the section on uptake, distribution and mode of action, exceptions are also possible here.

The information on breakdown, transformation, and metabolism forms an essential basis for the assessment of the residue situation. These data are usually generated by means of radioactive labelled active ingredients.

Information on the scope of the necessary examinations is given in the following guidelines:

- BBA Guideline Part IV, 3-2, "Testing the Residue Behaviour -"

Fate of Plant Protection Products in and on Plants - Metabolism, Metabolizing and Breakdown (Metabolism Guideline - Plant) -"

- BBA Guideline Part IV, 3-2/1, "Testing the Residue Behaviour - Quick Test of the Metabolizing and the Breakdown of Organic Active Ingredients of Plant Protection Products in Plant Cell Cultures -"

The evaluation procedures are attached as flow diagrams 6a und 6b.

An assessment is not possible if

- no corresponding test reports are available
- the suspension cell culture tests were not conducted with cells of the crops soybeans and wheat
- larger metabolite fractions have not been characterized, with larger metabolite fractions being meant those that have a portion of > 10 % based on the recovered radioactivity or > 0.01 mg/kg in the plant material examined
- a transfer of the results from one crop group to another is not shown to be possible.

If an authorization is sought for the application of a product in different crops, metabolism studies have to be conducted for one relevant crop from each group of crops. If studies are available for crops from three of these groups and the results indicate that the route of degradation is the same in all three groups then the transfer of the results is demonstrated and it is unlikely that any more studies will be needed. First hints of a possible transfer of the results are given by the plant cell culture tests.

#### Assessment

Assessment of suspension cell culture tests on the basis of BBA Guideline Part IV, 3-2 and 3-2/1 (flow diagram 6a).

The suspension cell culture test is obligatory for all organic active ingredients in plant protection products. If the studies in the wheat and soybean cultures lead to a different behaviour, no comparability of the results of one crop to the other can be assumed. More extensive metabolism studies are to be carried out on selected representatives of each crop group for which a

registration is sought. If the active ingredient proves to be persistent, **the authorization is for the time being called in question**. A comparison with the longevity in other environmental compartments **and a risk-benefit analysis** must be performed. More extensive studies are necessary for active ingredients that are used for plants or plant products used as food for humans and/or feed for animals.

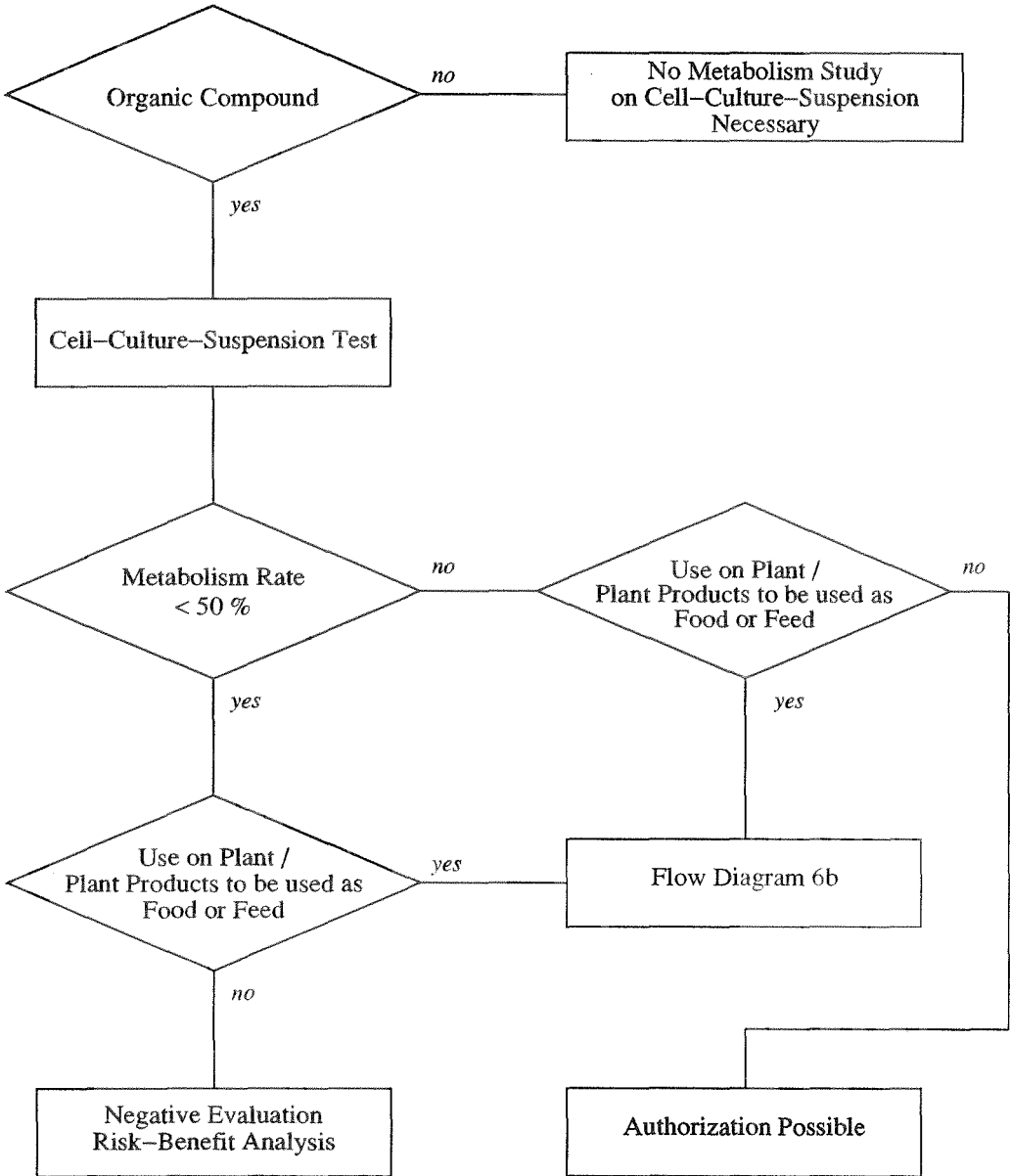
Assessment of more extensive metabolism studies is performed on the basis of BBA Guideline Part IV, 3-2 (flow diagram 6b).

If residues of an active ingredient and/or its metabolites occur, which are toxicologically unacceptable according to their nature and amount, the registration is **not possible (cut-off criteria)**. The toxicological acceptability is derived from the testing of the behaviour with regard to acute, sub-chronic and chronic toxicity, the mutagenic, embryotoxic, carcinogenic effects, influence on fertility, as well as from the behaviour in metabolism studies in animals and humans. Since the metabolism here cannot be influenced by external factors, its regulation by use restrictions is also not possible. For further assessment, therefore, further special toxicological studies with the active ingredient and/or its metabolites would have to be performed, or it would be necessary to dispense with use on plants or plant products. If the active ingredient proves to be persistent also in these studies, **the registration is for the time being called in question**. A comparison with the longevity in other environmental areas **and a risk-benefit analysis** must follow.



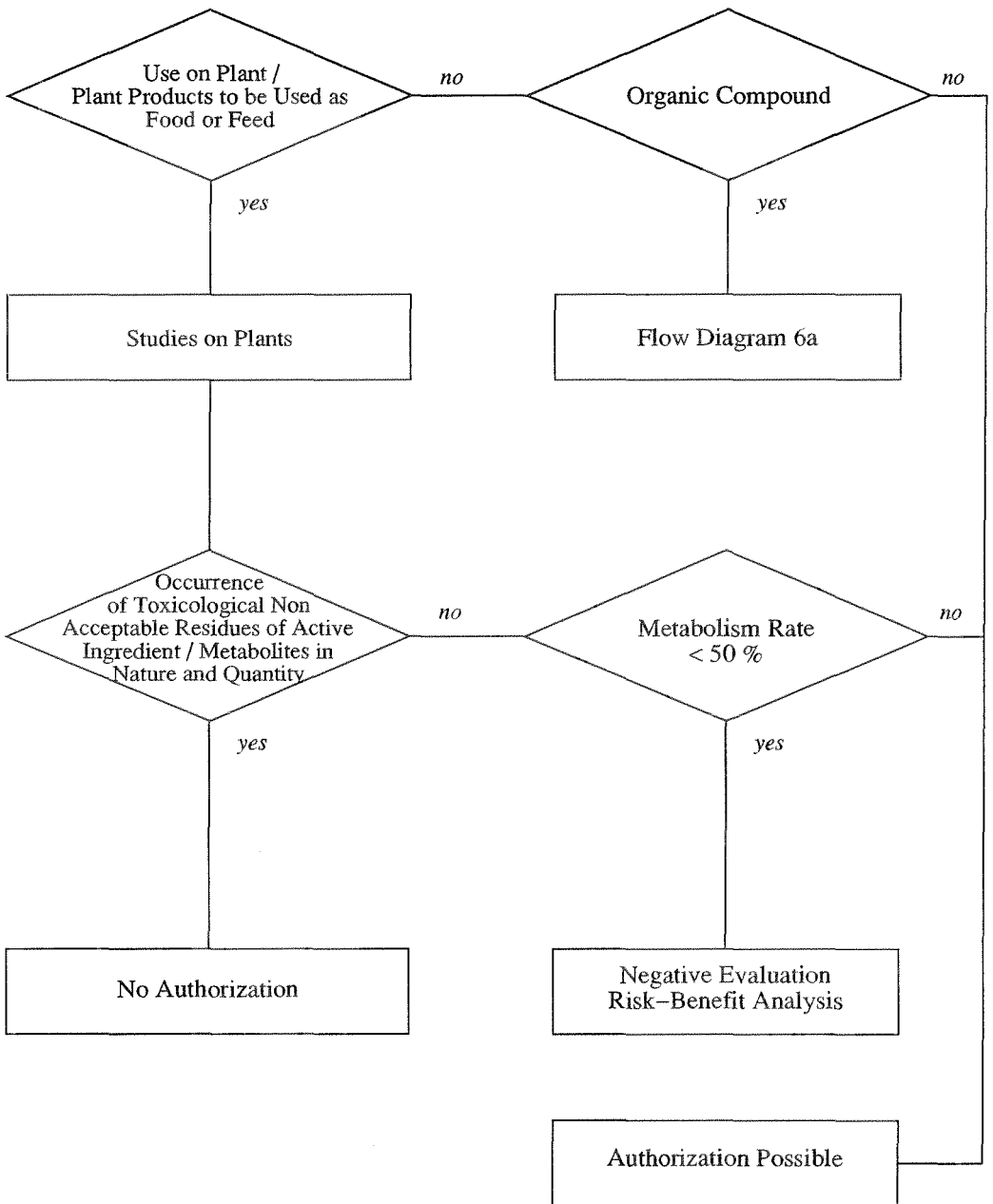
### Evaluation of the Metabolism – Cell–Culture–Suspension Test

BBA – Guidelines Part IV, 3–2 and 3–2/1



### Evaluation of the Metabolism – further Metabolism Studies

BBA – Guidelines Part IV, 3-2 and 3-1



#### **6.4 Residues in food and feed of plant origin**

The residue situation is examined in supervised trials. The most unfavourable conditions which are possible for use are selected (worst case). This worst case is defined as test conditions which in predictable circumstances will accommodate even the highest residues which may reasonably arise (maximum number of intentional applications, use of the maximum envisaged dosage), but which remain representative of conditions encountered in practice (test covering more than one growth period, but, as a rule, not more than two, account taken of regions where target plants are the principal crop, effect of choice of variety, routine methods of application and timing of application). The test results form the basis for establishing pre-harvest intervals and maximum residue limits for foodstuffs, but also for use restrictions for the protection of the consumer.

This regulatory work serves to limit dangers that could emanate from the unavoidable residues.

Information on the scope and realization of the required investigations is given in the following guidelines:

- BBA Guideline Part IV, 3-3, "Testing of residue behaviour - General information on design, preparation and realization of residue tests -"
- BBA Guideline Part IV, 3-3.1.1, "Design and preparation of residue tests - Testing the residue behaviour in grain exclusive of maize -"
- BBA Guideline Part IV, 3-8, "Testing residue behaviour - crops to be analyzed -".

As a rule the studies are required for all plant protection products used on plants or plant products and serving as food for humans and/or feed for animals.

The evaluation procedure is attached as flow diagram 6c.

In the assessment no distinctions are made between food and feed of plant origin, since pre-harvest intervals and maximum residue limits are established and use restrictions issued for both food

and feed.

An assessment is not possible if

- the required tests have not been performed or the corresponding test reports are not available
- essential information is lacking in the test reports
- metabolites relevant by their amount or toxicology were not analyzed (see metabolism guideline)
- the residue analysis on which the test reports are based could not be assessed or were assessed negatively (see also chapter 3)

### Assessment

**Negative assessment of this scheme;**

**decision on authorization of an individual or all claimed uses depending on risk-benefit analysis.**

**The authorization is called in question if**

- the conditions of use in the supervised trial do not correspond to the Good Agricultural Practice stated in the authorization request
- an existing maximum residue limit can be exceeded
- the highest dose in feeding studies with farm animals is lower than the sum of the residues in feed.

Depending on the authorization request and according to the information already available

- the development of further residue trials,
- the change of a maximum residue limit,
- the change of a waiting period,
- the issue of a use restriction or
- the rejection of individual claimed uses or of the plant protection product are possible.

**Negative evaluation of this scheme;**

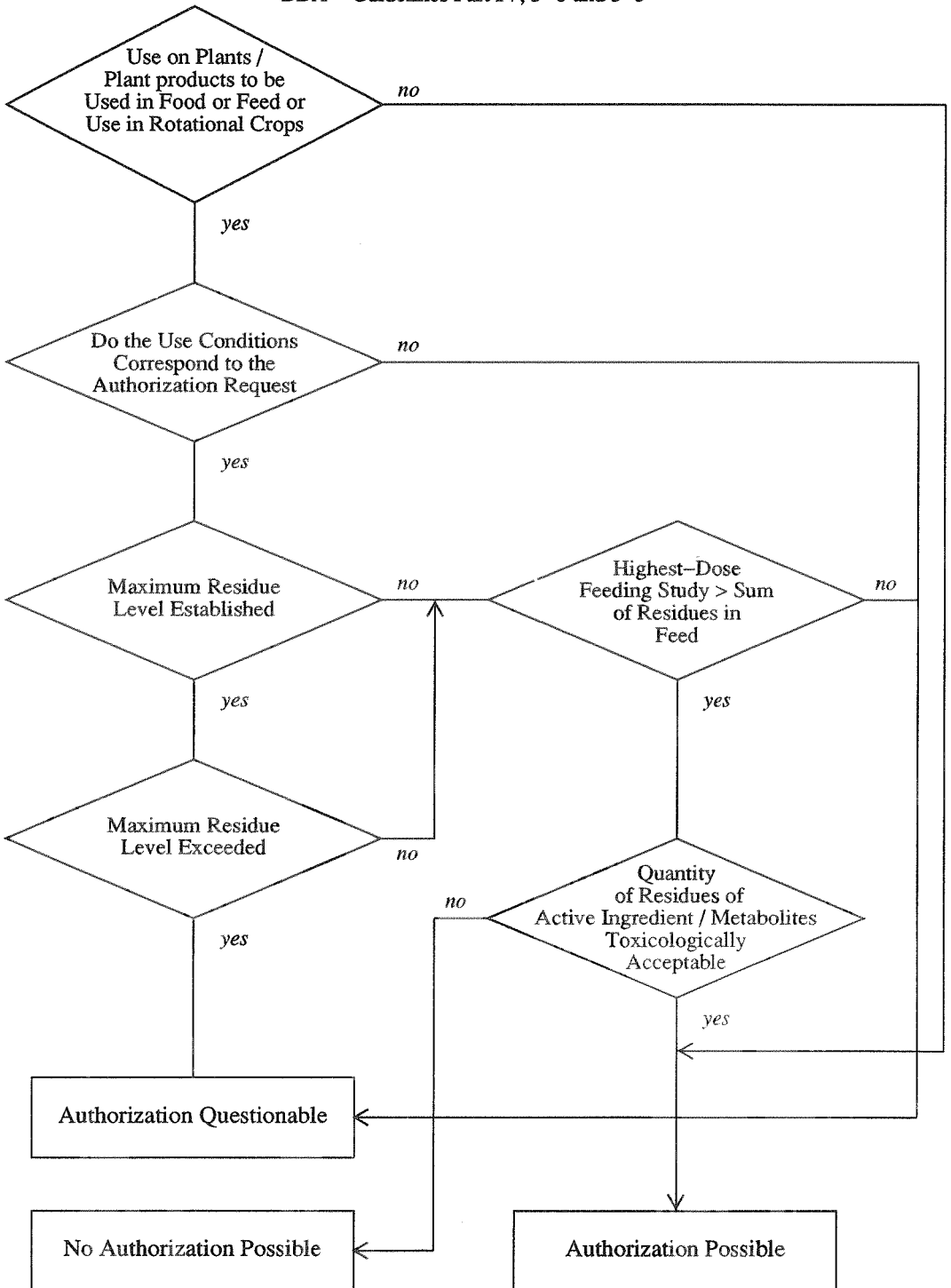
**individual or all claimed uses are restricted from authorization.**

**The authorization of a claimed use is not possible if the level of the residues of the active ingredient and/or metabolites is not acceptable from the toxicological point of view. The acceptability is derived from the results of the toxicological studies with regard to acute, subchronic and chronic toxicity, mutagenic,**

embryotoxic, carcinogenic effects, influence on fertility as well as to behaviour in the metabolism of animals and humans (see also assessment criteria toxicology).

# Evaluation of the Residues in Foodstuffs and Fodder of Plant Origin

BBA – Guidelines Part IV, 3–8 and 3–3



### 6.5 Residues in rotational crops

The guideline provides for a stepwise testing. This begins with a basic data file. The final stage requires supervised trials with all important rotational crops. The data are required for every plant protection product with which the rotation of plants serving as food for humans and/or feed for animals is possible.

The necessary data and the realization of the required studies are explained in the following guideline:

- BBA Guideline Part IV, 3-10, "Testing of residue behaviour of plant protection products in rotational crops (crop rotation guideline)"

With the following areas of use data on the residue situation in rotational crops are as a matter of principle not necessary:

- railroad herbicides
- non-cultivated land
- nurseries
- vine grafting
- storage protection
- permanent cultures

With permanent cultures, however, special attention is to be given to the accumulation of an active ingredient used as a result of annual application of plant protection products (see also point 5.6 of the guideline cited above). Further exceptions can arise from the possible exception arrangements in section 6.4.

The evaluation procedure is attached as flow diagram 6d.

An assessment is not possible if

- the necessary data are not available
- the required tests have not been performed or the corresponding test reports are not available.

### Assessment

The objective of the testing is, through a stepwise approach, to free from testing in the field those active ingredients for which an exposure of the rotational crops by residues can be ruled out.

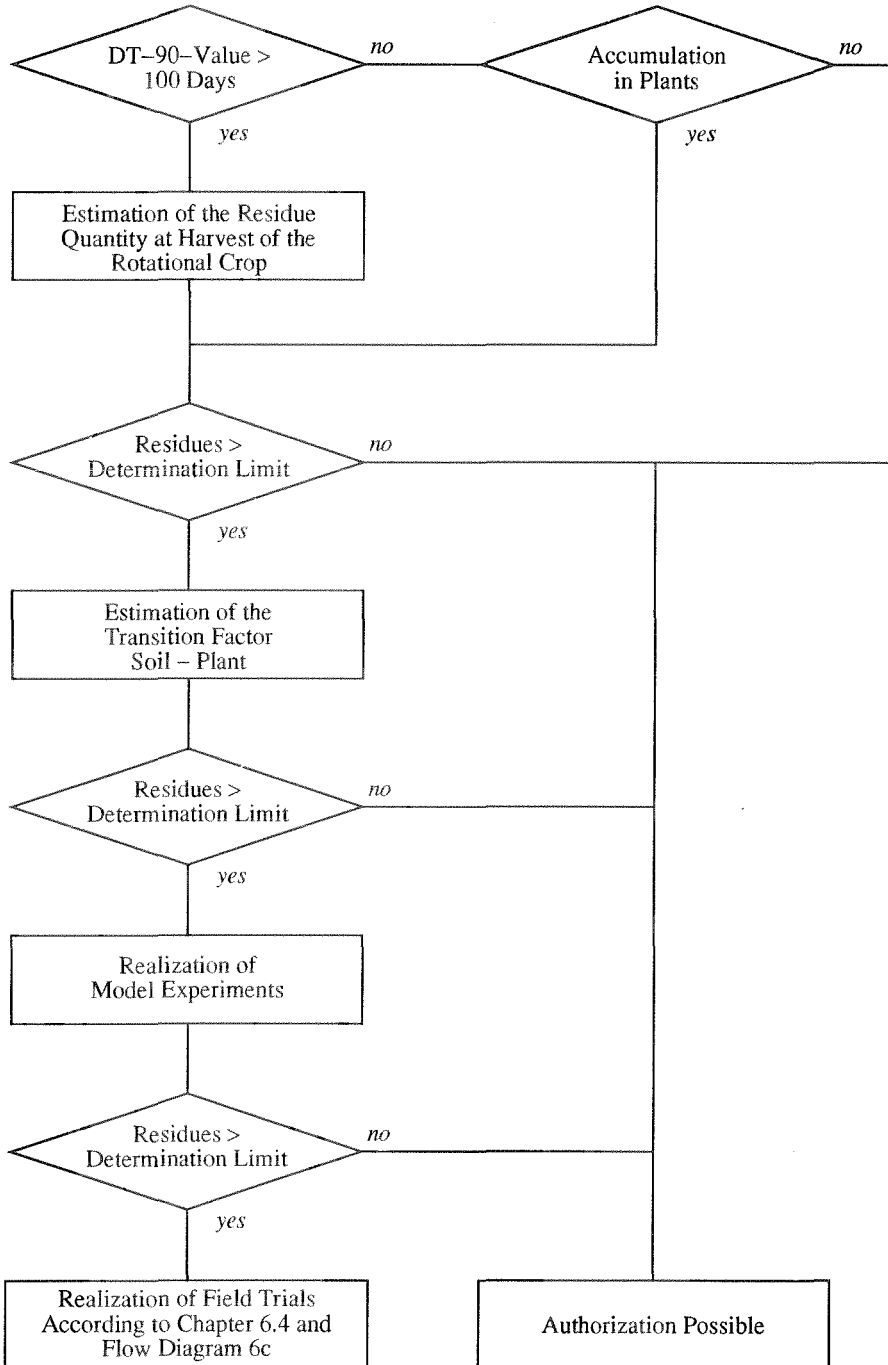
The assessment of the field trials that may become necessary is accomplished according to the same criteria that were also applied with treated cultures;

- maximum residue level suggestions for the rotational crop are worked out,
- pre-harvest intervals for the target culture are reconsidered and
- use restrictions for the rotating are issued.



### Necessity of Implementation of Residue Trials on Rotational Crops

BBA – Guideline Part IV, 3-10



## **6.6 Residues in prepared and processed plant products**

As a rule, the residue situation is examined in selected cultures of a culture group in two basic studies. Here the quantitative distribution of the residues over the various intermediate and end products is to be studied. In addition, a more realistic estimate of the intake of residues of active ingredients via the food is to be made possible. In individual cases the fixing of maximum residue levels in processed products is considered. The necessity for the studies depends on the significance of the processed products used for consumption by humans and animals, the level of the residues in the plants or plant products being processed, and the physical-chemical properties of the active ingredients. As a rule, no basic studies are necessary if residues in the plant or plant product to be processed are not detectable or if residues are detectable, but the plant or plant product will nearly always be eaten unprocessed. On the other hand processing studies (two basic studies and four follow-up studies) are always necessary if residues in the plant or plant product to be processed are detectable and processed products are of great significance for consumption by humans and animals. In all other cases it can be taken as an estimate for the need of processing studies that the TMDI value (Theoretical Maximum Daily Intake) does not exhaust the ADI value (Acceptable Daily Intake) by more than 10 %. This estimate is depending on the knowledge about the active ingredient as for example the physical-chemical properties. At least processing studies are necessary if the TMDI value exceeds the ADI value.

Information on the scope and realization of the required studies are given in the following guidelines:

- BBA Guideline Part IV, 3-4, "Testing the residue behaviour - Residue tests on processed plant products (processing guideline)-"
- BBA Guideline Part IV, 3-3.4, "Testing the residue behaviour - Studies on grape must and wine -"

The evaluation procedure is attached as flow diagram 6e .

An assessment is not possible if

- the required tests have not been performed or the corresponding test reports are not available

- essential data are lacking in the test reports
- relevant metabolites were not analyzed (see also chapter 6.3)  
(These metabolites should be taken into consideration in the residue studies.)
- the residue analysis on which the test reports are based could not be assessed or were assessed negatively (see also chapter 3)

### Assessment

**Negative assessment of this scheme;  
decision on authorization of an individual or all claimed uses  
depending on risk-benefit analysis.**

**The authorization is called in question if**

- an existing maximum residue level can be exceeded.
- an undesirable accumulation takes place in some products during processing. The acceptance is strongly correlated with the acceptance of the results of the toxicological studies.
- the highest dose in feeding studies with animals is lower than the sum of the residues in processed products that serve as feeds.

Depending on the registration request and according to the information already available

- the development of further residue tests,
- the change of a maximum residue level,
- the change in a waiting period,
- the issue of a use restriction,
- the rejection of individual claimed uses or of the plant protection product are possible.

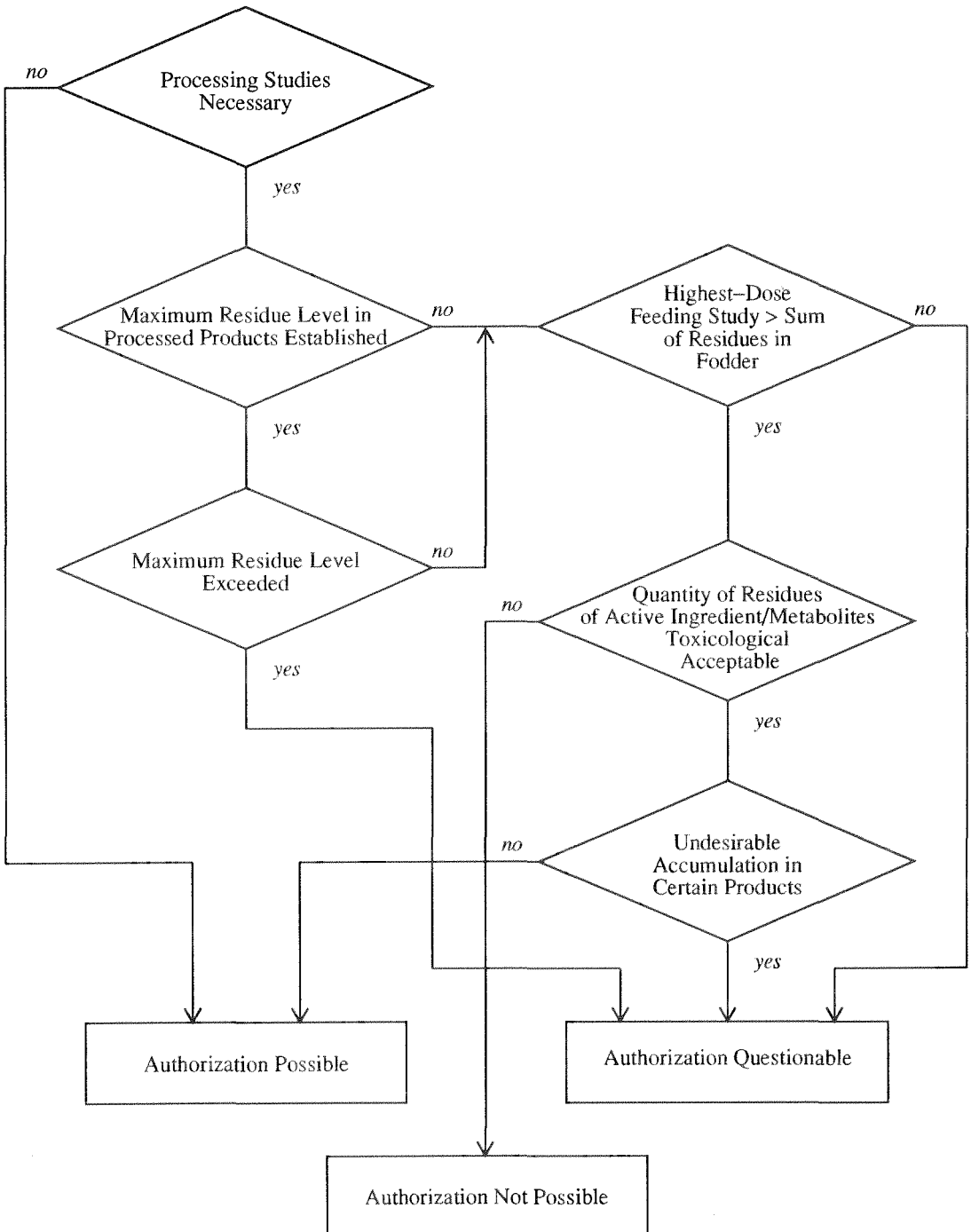
**Negative evaluation of this scheme;**

**individual or all claimed uses are restricted from authorization.**

**The authorization of a claimed use is not possible** if the level of the residues of the active ingredient and/or the metabolites is not acceptable from the toxicological point of view. The acceptability is derived from the results of the toxicological investigations with regard to acute, sub-chronic and chronic toxicity, the mutagenic, embryotoxic, carcinogenic effects, influence on fertility, as well as the behaviour in the metabolism in animals and humans (see also assessment criteria toxicology).

### Evaluation of Residues in Prepared and Processed Food and Feedingstuffs of Plant Origin

BBA – Guidelines Part IV, 3-4 and 3-3.4



### 6.7 Residues in food of animal origin after feeding residues-containing animal fodder

The data on residues in food of animal origin are worked out on the basis of metabolism studies and feeding studies with farm animals. It is possible here to work with radioactive labelled active ingredients and/or metabolites. Metabolism studies are necessary when relevant residues can occur in the animal fodder. Residues greater than 0.1 mg/kg are always relevant. In some cases, residues lower or equal than 0.1 mg/kg can also be relevant. Feeding studies are not necessary when the results from metabolism studies taking into consideration the residue levels in feedingstuff clearly indicate, that the lower limit of determination is sufficient as maximum residue limit for food of animal origin.

The results obtained in these tests form the basis for establishing slaughtering times and permissible maximum residue limits for animal foodstuff, but also for use restrictions for the protection of the consumer. Use in veterinary medicine is to be given appropriate consideration.

Special guidelines for testing the residue situation in food of animal origin do not exist at present. Information on the nature and extent of the data required is provided in the following guidelines:

- BBA Guideline Part IV, 3-1, "Testing of residue behaviour - General information on nature and extent of the required studies/ documents -"
- OECD Guidelines for Testing of Chemicals, Section 4, no. 417, "Toxicokinetics."

The data are required for every active ingredient the use of which leads to relevant residues in potential feed.

The evaluation procedure is attached as flow diagram 6f.

An assessment is not possible if

- the required tests have not been performed or the corresponding test reports are not available

- essential data are lacking in the test reports
- relevant metabolites were not analyzed (see also chapter 6.3).  
(These metabolites should be taken into consideration in the residue studies.)
- the residue analysis on which the test reports are based could not be assessed or was assessed negatively (see also chapter 3)
- data on metabolism in laboratory animals are not available.

### Assessment

**Negative assessment of this scheme;**

**decision on authorization of an individual or all claimed uses depending on risk-benefit analysis.**

**The authorization is called in question if**

- an existing maximum residue limit can be exceeded
- an accumulation can occur.

The acceptability is strongly correlated with the results of the toxicological studies.

Depending on the authorization request and according to the information already available

- the development of further residue tests,
- the change of a maximum residue limit,
- the change of a waiting period,
- the issue of a use restriction or
- the rejection of individual areas of application or of the plant protection product are conceivable.

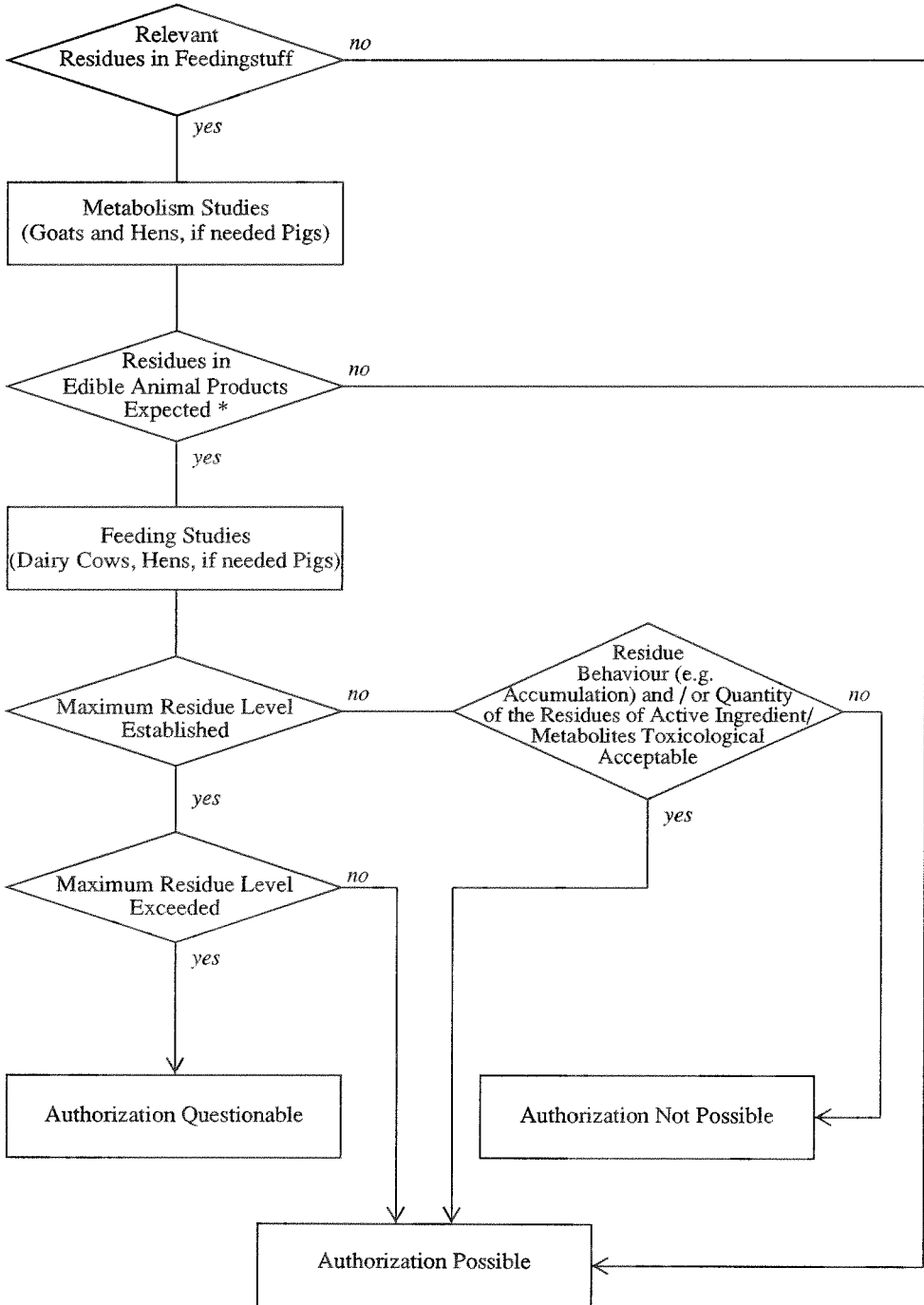
**Negative evaluation of this scheme;**

**individual or all claimed uses are restricted from authorization.**

**The authorization of a claimed use is not possible if the level of the residues of the active ingredient and/or metabolites is not acceptable from the toxicological point of view. The acceptability is derived from the results of the toxicological studies with regard to acute, subchronic and chronic toxicity, mutagenic, embryotoxic, carcinogenic effects, influence on fertility as well as from the behaviour in the metabolism of animals and humans (see also assessment criteria toxicology).**

# Evaluation of the Residue Situation in Foodstuffs from Animal Origin after Feeding Residue-Containing Animal Fodder

BBA – Guideline Part IV, 3-1 and OECD-Guideline 417



\* Expection is correlated with limit of determination; see above, need for feeding studies

### **6.8 Maximum residue limits and waiting periods**

Information on the procedure in establishing waiting periods and maximum residue limits is provided in the following guideline:

- BBA Guideline Part IV, 3-6, "Testing of residue behaviour - evaluation of residue studies: Waiting periods and proposals for maximum residue limits -."

The necessary risk assessment is described in detail in the following guidelines and publications:

- "Guidelines for predicting dietary intake of pesticide residue," WHO, Geneva 1989
- R. Hans and H. Hübner, "Establishing maximum residue limits for residues of plant protection products in/on foodstuffs - Estimate of intake of residues with food," Bundesgesundhbl. 5/92, pp. 246-250
- BBA Guideline Part IV, 3-7, "Testing of residue behaviour - Estimating the intake of residues of plant protection products with food -" (in preparation).

For the procedure for applying for an import tolerance see:

- BBA Guideline Part IV, 3-1, "Testing of residue behaviour - General information on nature and extent of the required studies/documents -"
- "Announcement regarding the procedure for establishing maximum residue levels in and on food for plant protection products not authorized in the Federal Republic of Germany but used abroad" dated 16 October 1991, Bundesanzeiger No. 202, p. 7286, 29 October 1991.

As a rule, the data are required for all plant protection products that can lead to residues in food and feed. The objective here is to develop proposals for maximum residue limits and waiting periods for new active ingredients or for uses claimed for the first time in the authorization, and to examine the existing standards for registered active ingredients.

The fixing of a permissible maximum residue limit takes place by the Federal Health Minister. Examination is the task of the Federal Health Office as subordinate federal authority.



The Federal Biological Research Centre for Agriculture and Forestry submits a proposal for a maximum residue level to the Federal Health Office. This proposal contains the maximum residue level required according to the residue data and taking into consideration "Good Agricultural Practice." The Federal Health Office examines the toxicological defendability of the proposal and, if appropriate, introduces the procedure for inclusion of the maximum residue level in the Rückstands-Höchstmengenverordnung (Maximum Residue Limits-Regulation).

In clarifying the question which metabolites are to be included in fixing maximum residue limits (MRL), in addition to the toxicological assessment of the metabolites the possibilities and the limits of food monitoring and cost/benefit estimates are also to be taken into consideration. In the toxicological assessment a comparison of metabolism in animals (rat) and in the plant is made. Combination effects with other plant protection products are taken into consideration. According to the arrangements of the FAO/WHO, the inclusion of metabolites in the MRLs regulation is to be restricted to the extent absolutely required (single compound concept). As a rule, in fixing MRLs only those metabolites are included that do not occur in animal metabolism or of which it is known, or of which it can be assumed that toxicologically they are more hazardous than the active ingredient, and which therefore as a rule require separate toxicological studies.

Two statistical methods for calculation of proposal for MRLs are described in BBA Guideline Part IV, 3-6. In addition, methods are offered for

- being able to identify outliers,
- being able to interpolate missing residue data when the waiting period is given and
- being able to calculate the waiting period when the MRL is given.

MRLs and waiting periods are divided into classes. In addition, at this point a risk assessment is also necessary in the form described by R. Hans and H. Hübner. This is a matter of conversion of the corresponding guideline of the FAO.

The fixing of a waiting period is orientated essentially to the most unfavourable residue case and Good Agricultural Practice, and is frequently prescribed by the time of application and/or the harmful organism to be controlled. Variations are only obtained to a limited extent. Where this latitude is available, it is used in the assessment and drafting of a proposal for MRLs.

A possible or actual exceeding of a permissible MRL always assumes utilization of the latitude given by the waiting period.

On the other hand, permissible MRLs are not permanently fixed values. A change is possible under the precondition of toxicological acceptability. Thus here too a raising or lowering of the permissible MRL can lead to a change in the authorization, even if the waiting period no longer permits any latitude.

The assessment of the residue behaviour of a plant protection product is inseparably connected to the assessment of the effects on the health of humans and animals. The decisions in this area are therefore always made with the approval of the Federal Health Office.

The evaluation procedure is attached as flow diagram 6g.

An assessment is not possible if

- the required tests have not been performed or the corresponding test reports are not available (residues in food and feed of plant origin, in rotational crops, in prepared and processed plant products, in food of animal origin)
- essential data are lacking.

#### Assessment

**Negative assessment of this scheme;  
decision on authorization of an individual or all claimed uses  
depending on risk-benefit analysis.**

**The authorization of the plant protection product is called in question if**

- the TMDI value (theoretical maximum daily intake) exceeds the ADI value (acceptable daily intake)

- the EMDI value (estimated maximum daily intake) exceeds the ADI value.

Depending on the authorization request and according to the information already available

- the development of further data on the residue behaviour,
- the change in a MRL ,
- the change in a waiting period,
- the issue of a use restriction or
- the rejection of individual claimed uses or of the plant protection product are possible.

**Negative evaluation of this scheme;**

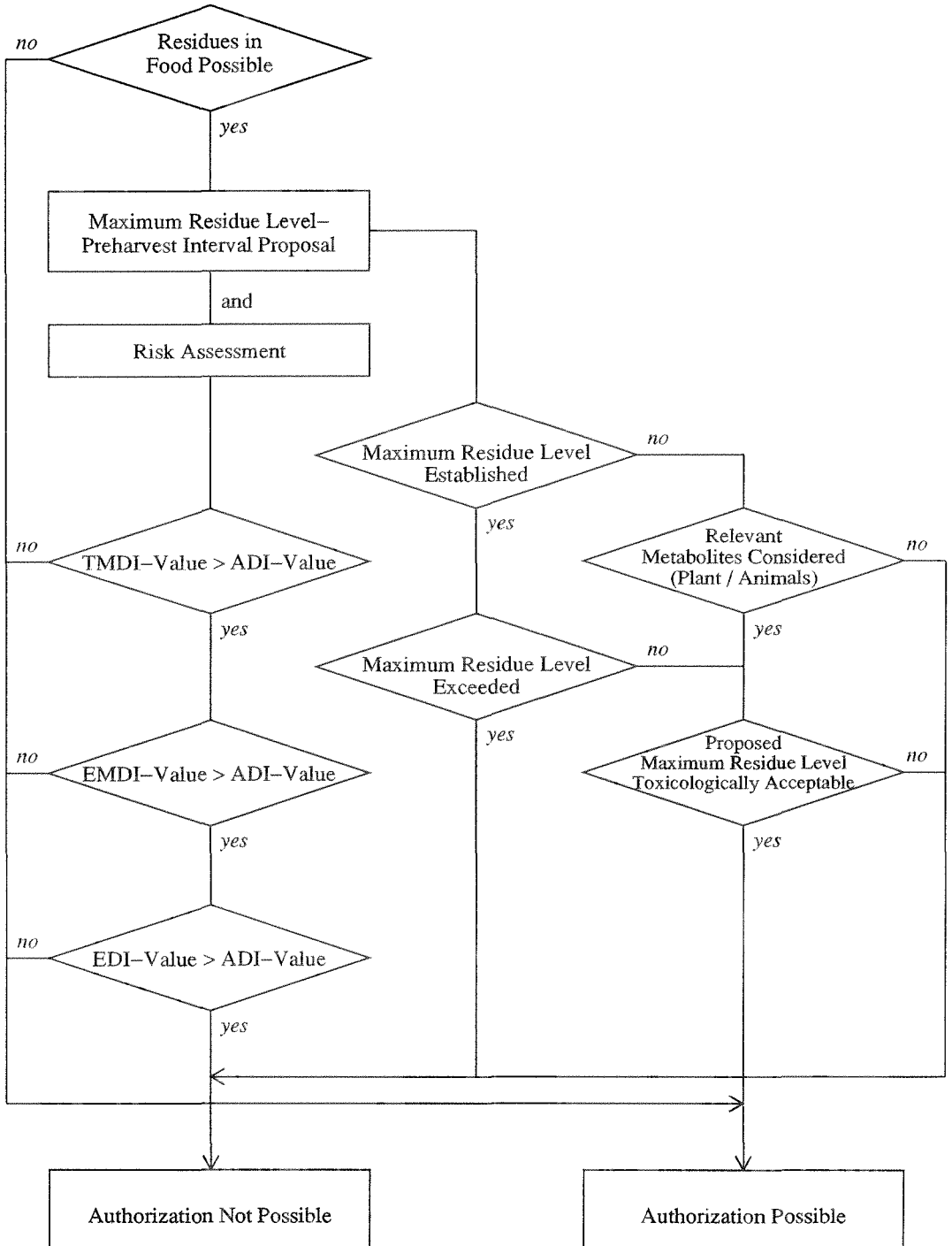
**individual or all claimed uses are restricted from authorization.**

**The authorization of the plant protection product or of individual claimed uses is not possible if**

- an already existing MRL is exceeded. It should be borne in mind here that the MRL regulation is conclusive, i. e. that a MRL exists for every combination of crops and active ingredients.
- there is a formation of relevant metabolites in plants that occur only in slight amounts, if at all, in the animal organism. The qualitative detection suffices here. In this case the metabolites must be included in the residue studies and in the residue definition.
- the EDI value (Estimated Daily Intake) exceeds the ADI value.
- the proposed MRL is not acceptable from the toxicological point of view. The acceptability is derived from the results of the toxicological studies with regard to acute, sub-chronic and chronic toxicity, the mutagenic, embryotoxic, carcinogenic effects, influence on fertility as well as to the behaviour in the metabolism of animals and humans (see also assessment criteria toxicology).

### Derivation of Maximum Residue Levels and Pre-Harvest Intervals

BBA-Guidelines Part IV, 3-6 and 3-7



R. Kloskowski, H.-G. Nolting, K. Schinkel

## 7. Fate in the soil

In the course of the authorization procedure for plant protection products there are also required test reports on the behaviour of the products in soil.

The execution of the corresponding studies is explained in the following guideline:

BBA Guideline Part IV, 4-1, "Fate of Plant Protection Products in Soil - Degradation, Conversion and Metabolism -"

Following products may be excluded from the studies described in this guideline:

- plant protection products for food storage such as  $\text{PH}_3$ , HCN,  $\text{CO}_2$
- products for wound-sealing and grafting

For the following products studies are required only to a reduced extent (e. g. orientational data) or upon request:

- seed dressings with an application rate of less than 100 g active ingredient/ha
- baits which are also intended for use in the field
- other plant protection products for food storage (e. g. baits), products for the treatment of potted cultures in the household, spray cans
- game repellents

In accordance with Guideline IV, 4-1, sufficient test documents for assessing the behaviour in soil are required.

According to step 1 of the Guideline (laboratory tests) an **assessment is not possible** in the case of

- non-presentation of a sufficient number (two or four) of degradation studies
- execution of the degradation and metabolism studies using soils that are not comparable with standard soils
- unsuitable test conditions, e. g. too high temperature during the execution of the tests

- lack of data on DT90 values
- lack of metabolism studies and lack of characterization of metabolites
- lack of data on bound residues
- lack of data on mineralization
- lack of laboratory degradation studies with relevant metabolites
- number of samplings within a degradation/metabolism study too low.

In accordance with step 2 of the Guideline (field tests) an **assessment is not possible** in the case of

- non-presentation of field studies
- test execution not in accordance with Guideline IV, 4-1
- lack of data on DT90 values
- lack of inclusion of relevant metabolites (as a rule the metabolites which are formed to > 10 % at any time of the study)
- execution of the tests at locations that with regard to climatic and soil data do not correspond to Central European conditions
- insufficient number of test locations (< 4 or < 6)
- number of samplings within a test too low
- execution of the tests with an unsuitable product (e. g. with regard to the proposed application rate, the type of formulation, the time of application)

### Assessment

The evaluation procedures on the behaviour in soil are shown in the flow diagrams 7a and 7b.

In the assessment a distinction is made between the persistence, i. e. the remaining residues of active ingredient and/or relevant metabolites in the soil and the metabolic pathway - especially with regard to the formation of bound residues.

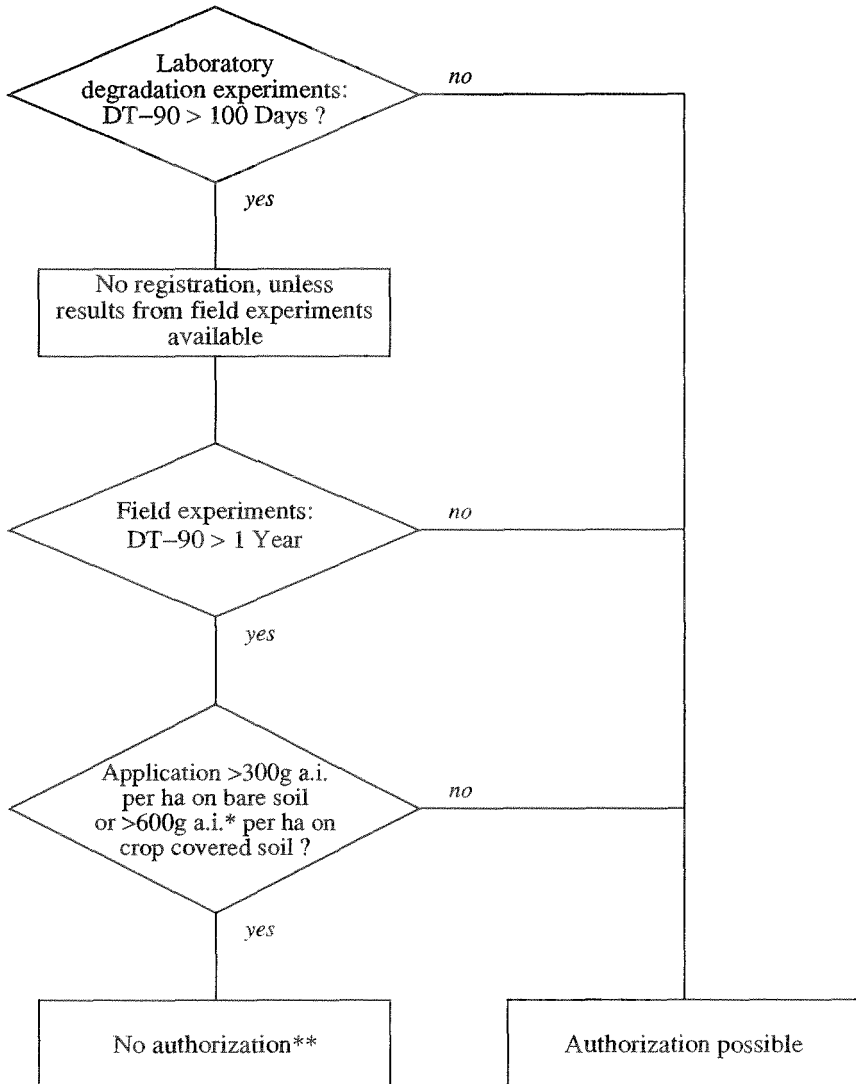
Provided that in the laboratory studies a DT90 value of more than 100 days is found and no field studies are conducted an authorization is not possible.

If in field studies after one year more than 10 % active ingredient and/or relevant metabolites are still present in the

soil, and a maximum application rate of active ingredient of more than 300 g/ha on bare soil or more than 600 g/ha on covered soil is intended, no authorization is possible, unless a risk-benefit analysis is conducted.

If in the metabolism study in the laboratory more than 70 % bound residues occur after 100 days, no authorization is possible, unless a risk-benefit analysis is conducted.

### Fate in Soil Degradation

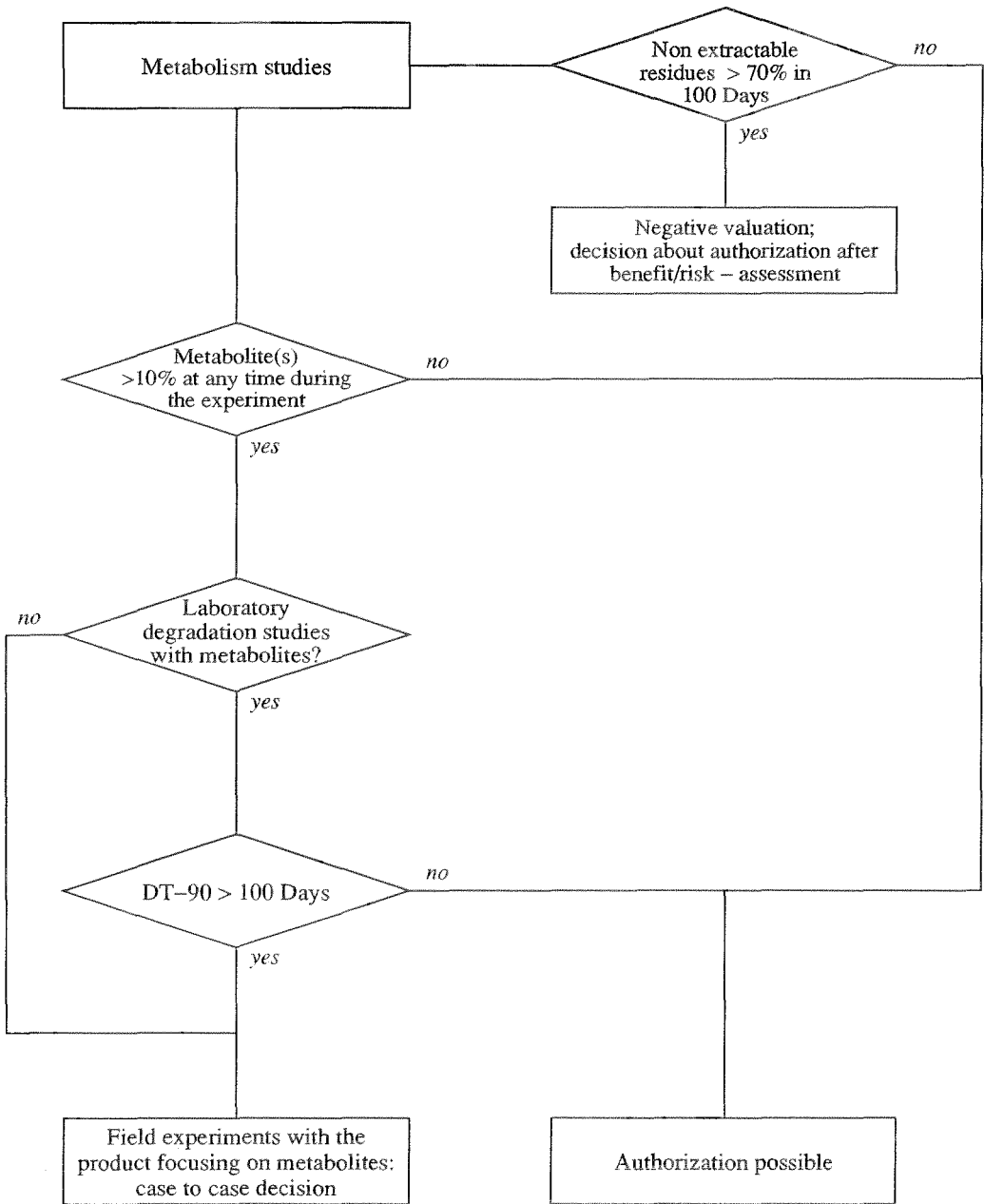


\* a.i.= Active ingredient; in case of multiple application within one vegetation period the total amount has to be considered

\*\* As far as the benefit/risk assessment gives any justifiable results concerning following questions: Accumulation in soil? Residues or phytotoxic damage to following crops? Influence on soil fauna and soil microflora? High probability that such effects will occur? Lack of mechanisms to compensate these effects? Negligible disadvantages resulting from nonapplication? Are other products available for the same purpose?



### Fate in Soil Metabolism



R. Kloskowski, H.-G. Nolting, K. Schinkel

### 8. Entry into the ground water

For the registration of a plant protection product it is also necessary to examine the movement of active ingredients and relevant metabolites in the soil and the possibility of leaching into the ground water.

The execution of the necessary investigations is described in the following guidelines:

1. BBA Guideline Part IV, 4-2, "Leaching behaviour of plant protection products"
2. BBA Guideline Part IV, 4-3, "Lysimeter investigations of the displacement of plant protection products into the subsoil"
3. Modification of the lysimeter guideline (Nachrichtenblatt des Deutschen Pflanzenschutzdienstes, 43(8), 183 (1991)).

The following products are excluded from the studies described in the guidelines:

- plant protection products for food storage such as  $\text{PH}_3$ ,  $\text{HCN}$ ,  $\text{CO}_2$
- products for wound-sealing and grafting

For the following products studies are required only to a reduced extent (e. g. orientational data) or upon request:

- seed dressings with an application rate of less than 100 g active ingredient/ha
- baits which are also intended for use in the field
- other plant protection products for food storage (e. g. baits), products for treatment of potted cultures in the household, spray cans
- game repellents

Test documents in sufficient number are required for assessing the leaching behaviour. An assessment is not possible if

in the laboratory investigations according to **Guideline IV, 4-2**

- the required tests have not been conducted or the corresponding test reports were not presented

- investigations were conducted with soils that do not correspond to BBA standard soils
- irrigation was carried out with an amount of water that does not correspond to that indicated or prescribed in the guideline
- tests with aged residues (aged leaching) are lacking, which in certain cases are required.

in the lysimeter studies according to BBA **Guideline IV, 4.3**

- the lysimeter does not correspond to the standards of the guideline with regard to the surface, depth, device for collecting leaching water
- in case of installation above ground great variations in temperature may cause falsified results
- the soil used does not correspond to the standards of the guideline
- the irrigation was not conducted according to the guideline
- not soil cores, but loosened soil were used
- the samplings (percolate and soil) deviate from the standards of the guideline and thus cause difficulties in the interpretation of the results in the sense of the statements made in the flow diagram
- the test was conducted under climatic conditions that are not comparable with Central European conditions (e. g. regarding temperature, precipitation)
- no studies have been conducted, although their necessity is clearly recognizable; protocol or interim report is lacking, if the studies are not yet finished
- the modification of Guideline IV, 4-3 (repeated treatment) was not taken into consideration.

**Assessment of movement into the subsoil on the basis of model calculations performed with the aid of physico-chemical parameters and the leaching results according to BBA Guideline IV, 4-2**

#### Assessment

The assessment according to the flow diagrams 8a and 8b (both diagrams have to be taken into consideration in the assessment) in certain cases provides for the requirement for lysimeter studies, the results of which lead to the following consequences:

1. Necessity for further studies:

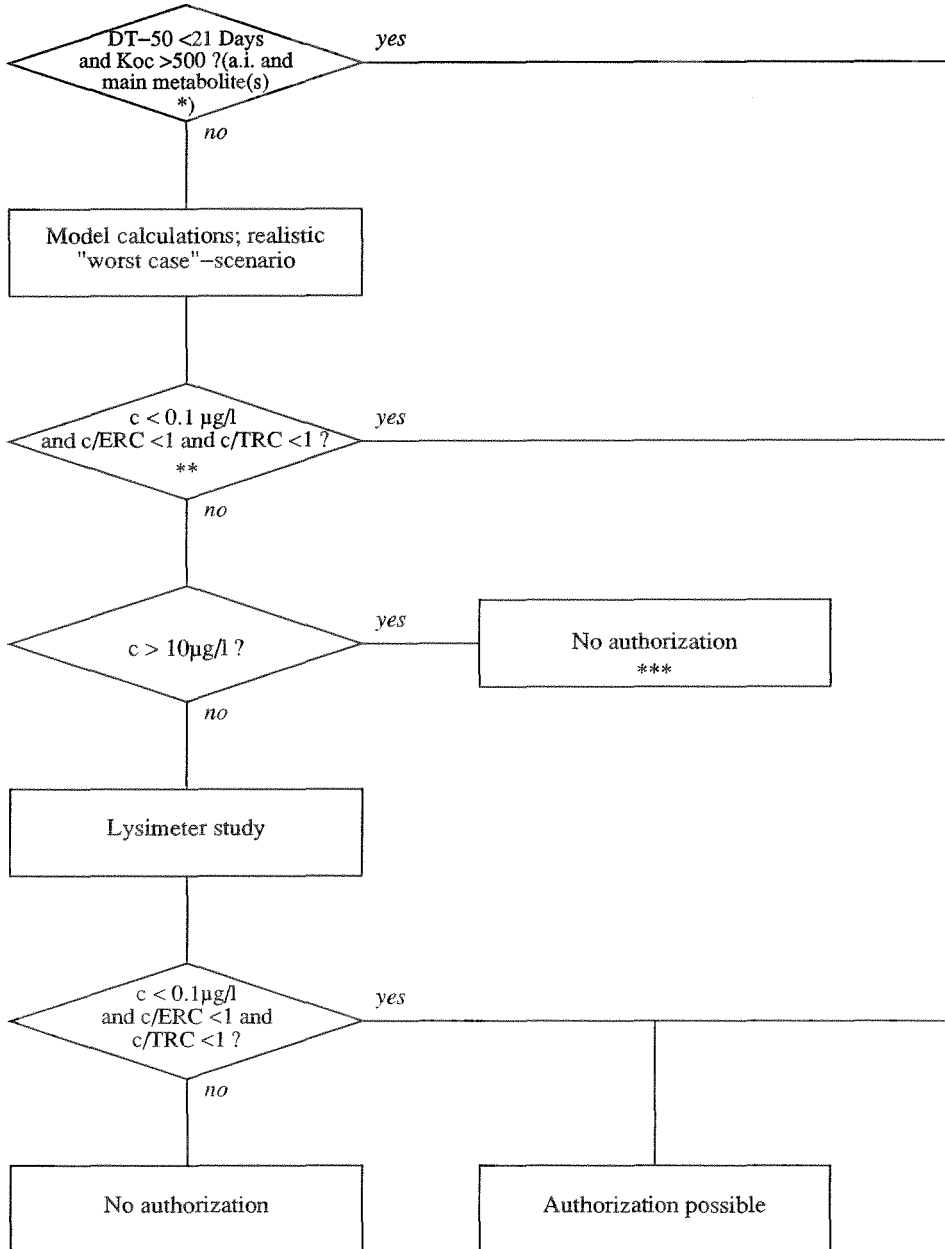
- If in the percolate of the lysimeters relevant metabolites occur in a concentration of more than 0.1 µg/l (mean value for the duration of the test) it has to be documented that they have no harmful effects on the ground water (e. g. effects on algae, bacteria, daphnia, fish, higher plants;  $c/ERC < 1$ ; see chapter 12) and that the concentrations are toxicologically acceptable for humans and (domestic) animals ( $c/TRC < 1$ ).

2. Negative assessment of the product (cut-off criteria):

- An entry of the active ingredient into the ground water of  $> 10 \mu\text{g/l}$  is simulated in the model calculations (e. g. PRZM/PELMO). \*)
- An entry of the main metabolite(s) into the ground water of  $> 10 \mu\text{g/l}$  is simulated in the model calculation, the harmlessness of which cannot be varified according to 1. \*)
- In the lysimeter tests the active ingredient is found in the percolate in a concentration of more than 0.1 µg/l (mean value for the duration of the test).
- In the lysimeter tests relevant metabolites are found in the percolate in a concentration of more than 0.1 µg/l (mean value for the duration of the test), the harmlessness of which for the ground water cannot be varified according to 1.

\*) It is up to the applicant to show e. g. by lysimeter studies that the active ingredient and/or the metabolite(s) do not cause harmful effects to the ground water.

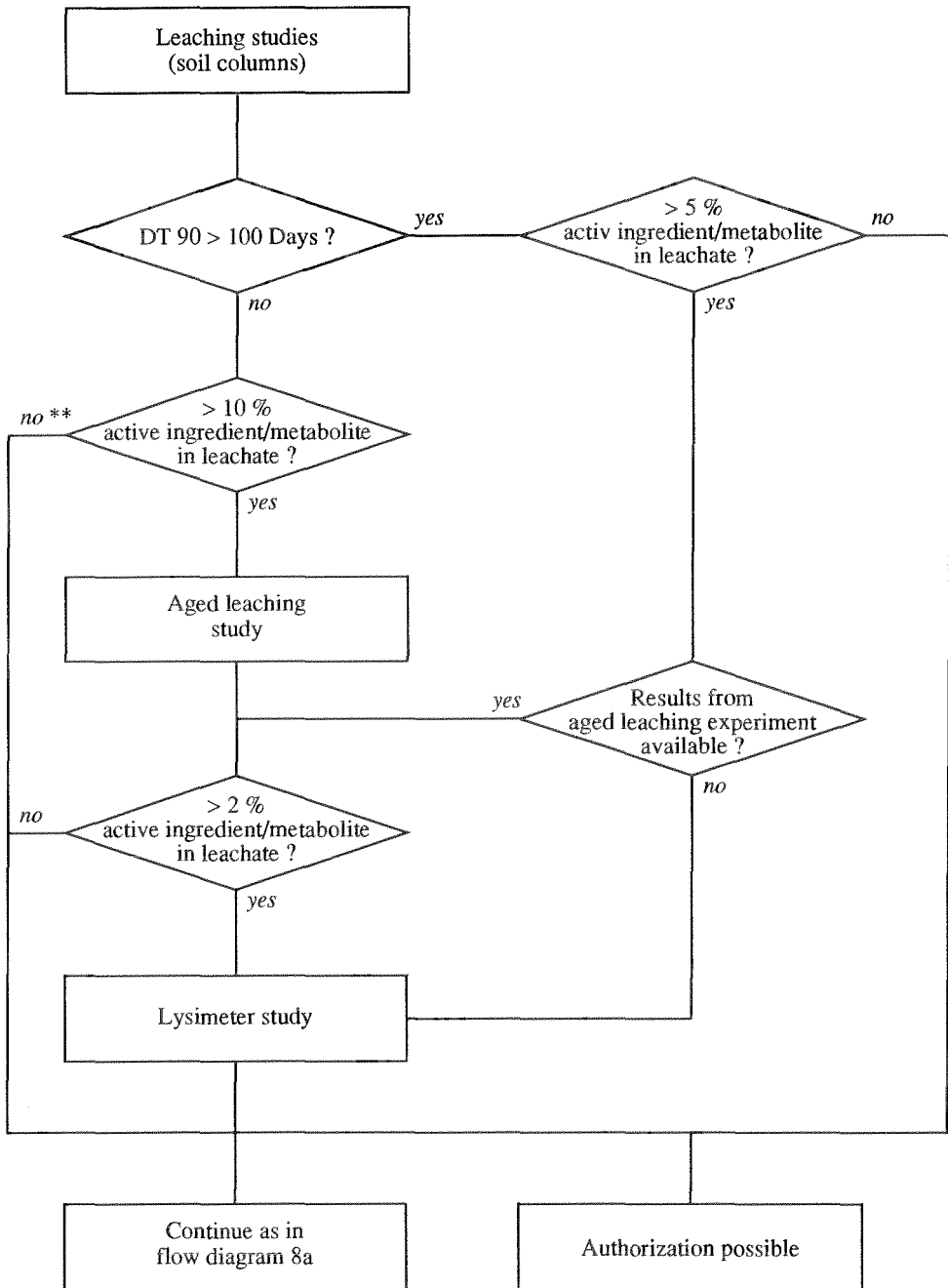
### Mobility and Leaching 1st Part (see also 2nd Part)



\* main metabolite: > 10% at any time during the metabolism study  
\*\* c = concentration in leachate  
ERC = Ecologically Relevant Concentration  
TRC = Toxicologically Relevant Concentration  
\*\*\* It is up to the applicant to show e.g. by lysimeter studies,  
that the active ingredient / metabolite(s) do not cause harmful effects  
to the ground water

### Mobility and Leaching

2nd Part (see also 1st Part)



\*\* For active ingredients which according to their high efficacy are used with very low application rates aged leaching experiments can be required even if the concentration in leachate is less than 10%

R. Kloskowski, H.-G. Nolting, K. Schinkel

### **9. Degradability and fate in the water/sediment system**

By drift, runoff or via drainage, plant protection products enter shallow surface waters. Investigations in water/sediment systems are intended to provide information on their behaviour.

The execution of the required studies is described in the BBA Guideline Part IV, 5-1 "Degradability and behaviour of plant protection products in the water/sediment system."

Excepted from the studies are products which in tests for ready biodegradability according to current EC or OECD guidelines (e. g. OECD 301 A-E) have been proven to be readily degradable.

In addition, studies are not necessary for plant protection products the formulation and/or proper use of which preclude any water contamination. This applies e. g. to:

- products for wound-sealing and grafting
- plant protection products for food storage
- rodenticides
- products which are used only indoors, including balconies
- products in spray cans.

An assessment of the product cannot be accomplished if:

- no data were presented
- the water and sediment selected for the studies deviate extensively from the standards of the guideline
- the execution of the tests, including acclimatization and recording of the necessary parameters for characterizing the water and sediment as well as with regard to the test conditions, deviates extensively from the guideline standards
- the number of samplings within the study was too low.

#### **Assessment**

The assessment of the results is conducted according to flow diagram 9. The transformation of the active ingredient in the

water as well as the distribution pattern between water and sediment and the behaviour in the sediment have to be taken into consideration.

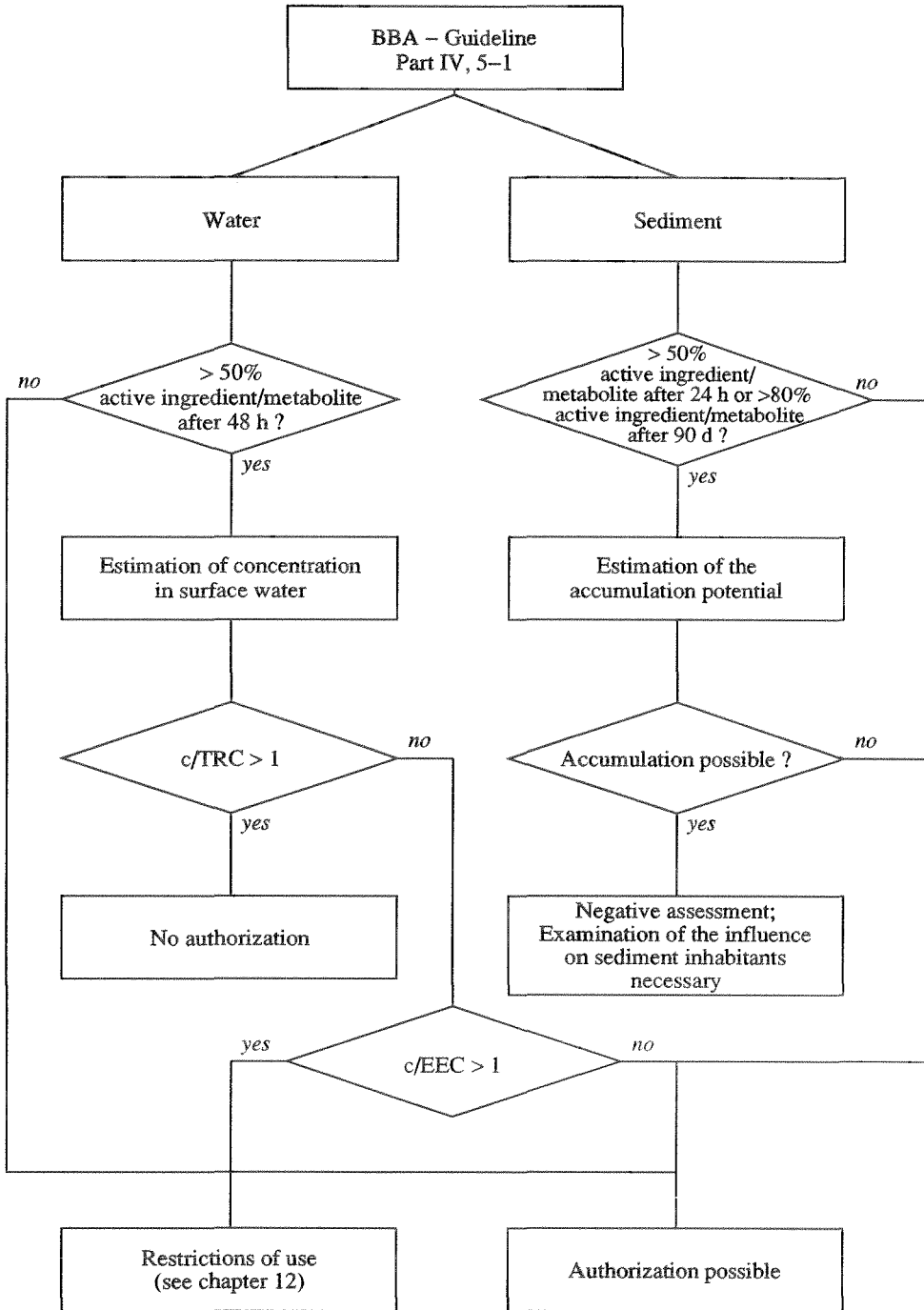
Active ingredients that prove to be persistent in **water** or form metabolites which, for their part, are persistent too (> 50 % active ingredient and/or > 50 % of the stoichiometric possible metabolite(s) after 48 hours) may, depending on application rate and application frequency, lead to potentially harmful estimated environmental concentrations ( $c/EEC > 1$ ; see chapter 12) in the surface water. In this case restrictions of use have to be considered (see chapter 12). If toxicologically relevant concentrations ( $c/TRC > 1$ ; see chapter 8) must be expected, an authorization is not possible.

In many cases there is a rapid movement of the active ingredient or its conversion products into the **sediment**. If such an incorporation into the sediment (> 50 % active ingredient and metabolites after 24 h) is combined with a slow degradation of the active ingredient or with its conversion to persistent metabolites so that after 90 days 80 % of the active ingredient or of the metabolites are still located in the sediment, an accumulation of residues in the sediment is possible. An authorization of products containing such active ingredients is possible only if adverse effects on the organisms living in the sediment can be precluded.

The results of the water/sediment studies also enter into the field of aquatic toxicity as supporting information. Corresponding tests of the toxicity of the active ingredient or of the metabolites for aquatic organisms, or examination of the effects on the benthos nevertheless can be considered to be necessary independent of the trigger values cited here.



### Degradation and Fate in Water/Sediment-System



c = Concentration in surface water  
EEC = Estimated Environmental Concentration  
TRC = Toxicologically Relevant Concentration

D. Gottschild, W. Storzer and A. Wilkening

#### **10. Volatilization and behaviour in the air**

Subject of the evaluation is the volatilization behaviour of the active ingredients of formulations used in practice from plant and soil surfaces. In case of high losses, the persistence of the active ingredients in question in the air is to be estimated.

BBA Guideline Part IV, 6-1 [1] "Testing of volatilization behaviour and fate of plant protection products in the air" serves as instructions.

The studies required by this guideline are explained in the following guidelines:

- BBA Leaflet 55 "Testing the behaviour of plant protection products in water" [2]
- OECD Draft - Test Guideline "Phototransformation of Chemicals in Water" [3]
- OECD Draft - Test Guideline on Photochemical Oxidative Degradation in the Atmosphere, "The rate of Photochemical Transformation of Gaseous Organic Compound in Air under Tropospheric Conditions," July 1991 [4]
- R. Atkinson, "Kinetics and Mechanisms of the Gas-Phase Reactions of the Hydroxyl Radical with Organic Compounds under Atmospheric Conditions", Chem. Rev. 86, 69-20 (1986) [5]

The test concept follows a step-wise approach (see diagram 10). It is first tested whether the active ingredient is sufficiently stable toward hydrolysis and direct photolysis in water in order to be able to reliably evaluate the volatilization of the active ingredients from their formulations as determined by indirect detection methods. The results of these studies mainly serve as exclusion criteria for the necessity of testing of the volatilization behaviour according to step 2. The tests on hydrolysis are to be performed according to [2], those on direct photolysis, according to [3].

If within the first 24 hours the volatility tests show a

volatilization rate of more than 1/5 of the originally applied amount, the extent of photochemical-oxidative degradability of the pure active ingredients in the air must be determined following step 3. The tests are to be performed according to [1].

It is also accepted to calculate tropospheric DT50 values with respect to gas-phase reaction with OH radicals. The estimation of rate constants for this reaction according to Atkinson's method is based on an annually and globally averaged 12-h daytime OH radical concentration of  $6 \cdot 10^5$  molecules  $\cdot$  cm<sup>-3</sup>. This estimation does not represent a "realistic worst case".

Substances showing DT-50 values of more than 2 days according to Atkinson's method are considered as persistent.

Despite a great tendency toward volatilization and high persistence in the air the product can be authorized if, on the basis of application pattern and the stability in/on plants, a sufficient decomposition of the active ingredient in soil and in water is assured.

### Assessment

#### - Negative assessment of the scheme

##### **No authorization of the product (cut-off criterion)**

- The product tends to volatilize (volatilization rate > 20 % in 24 h) and is persistent in the air. Persistent means that the DT50 value according to Atkinson's method exceeds 2 days. Because of the application pattern and the stability in/on plants, in soil, and in water a sufficient degradation of the active ingredient is not assured.
- The active ingredient tends to volatilization, is stable in air (see above) and, in addition, has an accumulation potential.

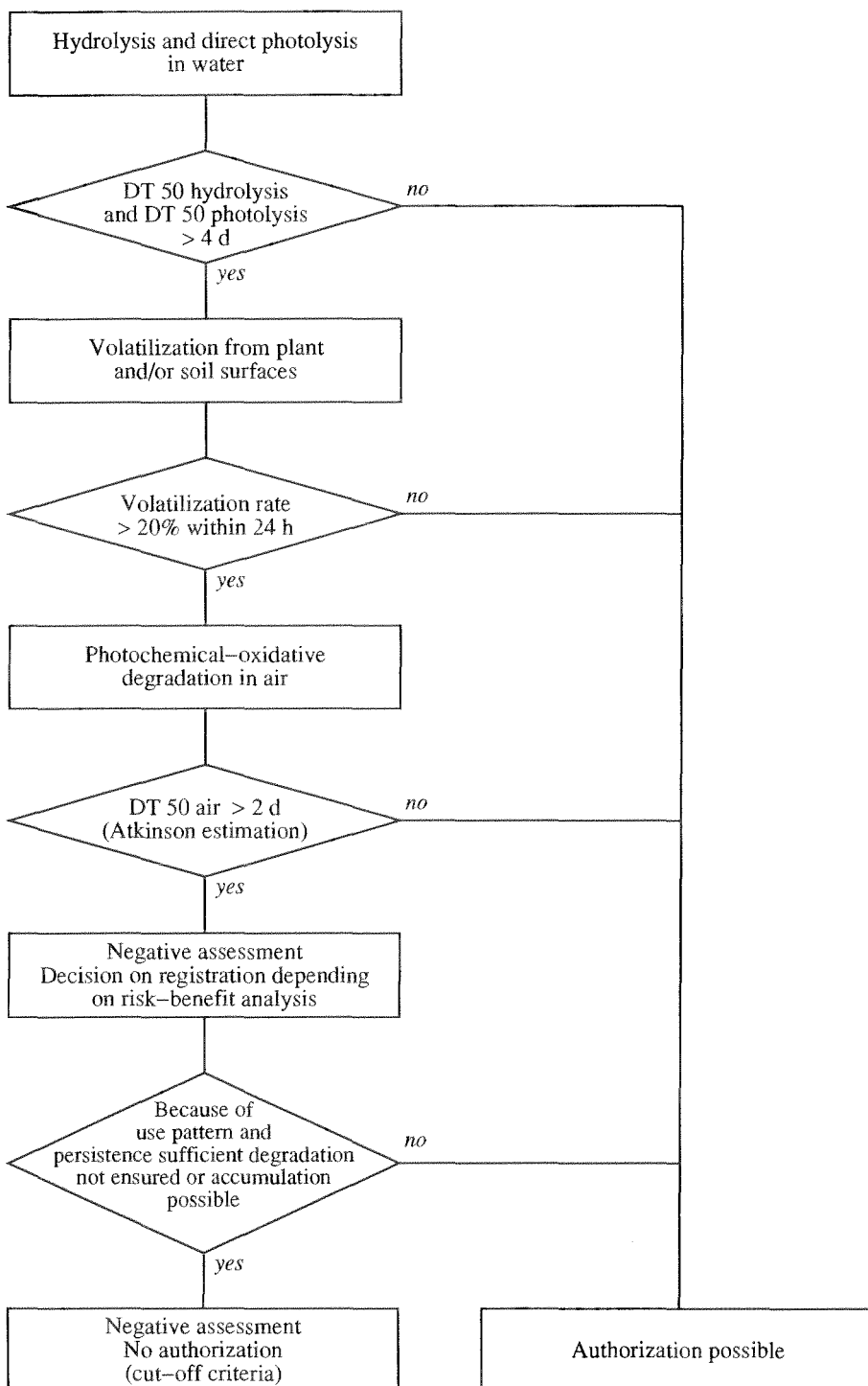
#### - Negative assessment of the scheme

##### **Decision on authorization depends on risk-benefit analysis**

- The active ingredient tends to volatilization and is stable in air (see above).

### Behaviour of Plant Protection Products in the Air

Examination according to BBA-Guideline Part IV, 6-1



G. Joermann, H. Köpp, A. Wilkening

## **11. Bioaccumulation**

In considering bioaccumulation a distinction is made between

- direct bioaccumulation where organisms acquire high concentrations of a substance out of the ambient medium and
- indirect bioaccumulation where organisms acquire high concentrations of a substance out of their food.

In both cases the accumulation can result in chronic contamination of organisms which can cause deleterious effects in these organisms or in the next link of the food chain.

Evaluation with regard to bioaccumulation is accomplished for all plant protection products. The required studies are described in the following guidelines:

- BBA Guideline Part IV, 5-1: Degradability and behaviour of plant protection products in the water/sediment system
- BBA leaflet 55: Testing the behaviour of plant protection products in water
- OECD Draft Test Guideline: Phototransformation of chemicals in water
- OECD Test Guideline 305 E: Bioaccumulation - Flow through fish test.

The evaluation is accomplished in tiers; in part it contains elements from other schemes. The course of the evaluation is presented in the appended diagram. In all steps, in addition to the active ingredient the relevant metabolites are also considered.

### **11.1 Stability in water and air**

If an active ingredient is very unstable in the environment, an accumulation potential can be precluded. This is assumed if in the water/sediment system both DT90 values are shorter than 10 days, and if in addition the half-lives for hydrolysis and for direct photolysis in pure water are shorter than 4 days. Bioaccumulation can also be precluded for those active ingredients that according

to current EC or OECD guidelines are classified as biologically readily degradable. If doubts exist regarding a rapid degradability, the evaluation proceeds according to the diagram.

### **11.2 Lipophilic properties**

As a rule, the n-octanol/water distribution coefficient ( $P_{ow}$ ) is used as a parameter. Other physical and chemical properties (molecule size, solubility in water, degree of ionization) likewise have an influence on the accumulation behaviour and, if appropriate, must be considered.

#### **11.3.1 Bioaccumulation in aquatic organisms**

For active ingredients that are not readily degradable and are lipophilic according to the criteria given in the diagram a bioaccumulation test with fish is required. The bioconcentration factor (BCF), the kinetics of uptake and the kinetics of elimination are evaluated.

The data derived for fish are not transferable without reservations to other aquatic organisms (invertebrates and algae), since the metabolizing and eliminating mechanisms are different. If data on other aquatic organisms are available, the assessment is thus far accomplished according to the scheme given for fish.

#### **11.3.2 Bioaccumulation in terrestrial organisms**

For assessing the bioaccumulation in mammals and birds, first the results of the toxicokinetic studies with laboratory rodents and, if available, with domestic animals are used. The following findings are to be interpreted as indications of bioaccumulation:

- low metabolizing rates
- high affinity to fat tissues
- long period up to the plateau of tissue concentration (> 1-2 weeks)
- slow elimination from organs (half-life > 3-5 d).

If such indications of bioaccumulation are present, tests are required that provide data for the bioaccumulation factor (BAF), i.e. the concentration ratio between tissue and feed in equilibrium. The necessity for bioaccumulation tests with birds is

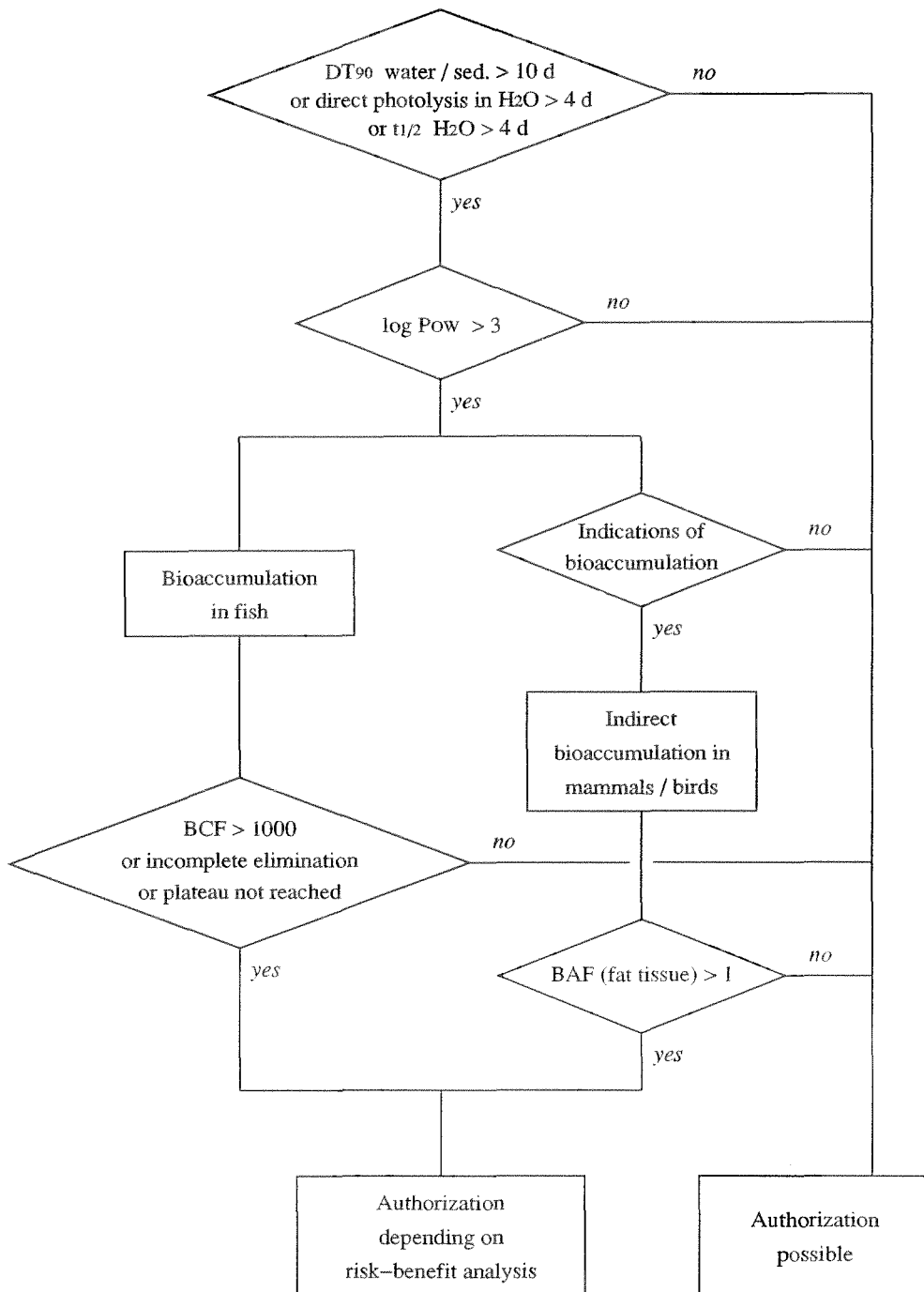
decided on a case-by-case basis. In assessing the data it is to be taken into consideration that the BAF value of a substance for birds as a rule is higher than for mammals, and for carnivorous species higher than for herbivorous or omnivorous species.

With other terrestrial organisms no tests on bioaccumulation are obligatory at the present time. If in-house or published data, e.g. for earthworms, are available, these will be taken into consideration in the decision.

### Assessment

- Evaluation in the scheme as "negative" (cut-off criteria, no authorization)  
Accumulation potential in conjunction with persistence of the active ingredient.
  
- Evaluation in the scheme as "negative" (authorization depending on risk-benefit analysis)  
Aquatic system
  - BCF > 1000 (whole body, wet weight)
  - plateau not reached during an exposure period of 14 days or more
  - elimination uncomplete (constant concentration in the last two samplings)Terrestrial system
  - BAF > 1 for mammals and birds, based on fat tissue

## 11. Bioaccumulation





H. Köpp

## 12. Side-effects on aquatic organisms

### 12.1 Introduction

According to Art. 21 para. 3 of the Plant Protection Act, data on the effects of the product on the environment are to be submitted with the application. The testing according to Art. 15, para. 1 has to clarify, among other things, whether the proper use of a product has indefensible effects on the ecology. The definition of the term environment in Art. 2, para. 1, 6 clarifies that both the structures of ecosystems (the organisms) and the functions (matter and energy turnover) are to be considered.

### 12.2 Scope of testing

For assessing possible effects in aquatic ecosystems aquatic ecotoxicology uses primarily the following laboratory tests and organisms:

Guideline	Organism	Duration	End points	Test substance
OECD 201	Plankton algae	72-96 h	Growth inhibition	W (P)
OECD 202,I	Daphnia magna	48 h	Mortality	W (P)
OECD 202,II	Daphnia magna	21 d	Mortality Reproduction Growth	W (P)
OECD 203	Rainbow trout carp or other species	96 h	Mortality	W (P)
OECD 204	Rainbow trout	21 d	Mortality Behaviour Growth	W (P)

[For log Pow > 3 or other indications of bioaccumulation potential:]

OECD 305 E	Rainbow trout or Bluegill sunfish		Uptake period up to steady- state, BCF, elimination	W
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W = Active ingredient (obligatory)

(P) = Formulated product if the product contains two or more active ingredients, or, e.g., in the case of EC and SC formulations. For details see BBA Guideline I, 1-2.

As a rule, tests performed according to other internationally recognized guidelines are also accepted (e.g. EPA: bioaccumulation in fish, early-life stage or life cycle tests).

Special regulations on the scope of the testing apply, for example, for certain seed treatment, wound-sealing, repellent and storage protection products as well as spray cans.

For details see BBA Guideline I, 1-2.

Tests for bacterial toxicity are not required at present.

Tests on other organisms (e.g. benthic organisms) or with relevant metabolites can be required in justified cases.

An assessment is possible only with complete and valid documents. Missing data lead to interruption of the authorization processing and possibly to rejection.

### **12.3 Exposure**

Contamination of surface waters can take place by means of spray drift, runoff, drainage or ground water or precipitation. Corresponding to currently available data spray drift is in the forefront of considerations regarding exposure. The basic values agreed upon among the BBA, BGA and UBA regarding spray drift were not selected in the sense of a theoretical worst-case assumption, rather with consideration to common agricultural practice and realistic situations.

The exposure assessment is performed for a stretch of standing water 30 cm deep. This corresponds to the conditions of many ditches and brooks as well as the bank zones of larger bodies of standing water. The area of the body of water is not prescribed, since also small bodies of water belong to the environment. Bodies of water of this depth are very frequent in the agricultural

landscape. This "standard water body" therefore does not represent any "worst-case scenario", rather a type actually affected by agricultural activity.

### 12.3.1 Spray drift

Spray drift is at present calculated according to the following basic values, which are referred to the maximum foreseen application rate (= 100 %):

Distance [m]	Time of application	Sediment on the water surface in [%]				
		Orchards		Viticulture		Hops
		V	F,D(*)	V,D	F(*)	F,V,D
5		10	15	4	6	11
10		4	6	1.5	2.25	7
[15		2	3	1	1.5	4.5]
20		1.5	2.25	0.5	0.75	3
30		0.7	1.05	0.2	0.3	1.5
40						0.6
50						0.2

Application times: F = only for early growth stages

V = only with full foliage; late stages

D = generally; treatment in early and late stages

For treatment in hops as well as in orchards and vineyards with full foliage the model is thus completed. Since in orchards and vineyards the test for early growth stages are still lacking, until further notice the provisional basic values indicated by (\*) apply here.

For applications with portable equipment (like knapsack sprayers) to low-growing crops (e.g. strawberries, cabbages) the viticultural values (full foliage) are used. Applications where the hand-held sprayer is kept more horizontal or even points upward (cane fruit, climbing french beans, etc.), assessment will be on a case-by-case basis, since here no generalizing data are currently available.

For field spraying equipment in agriculture it can be assumed, based on the current data situation, that at a spacing of more than 10 m no noteworthy sediment occurs. This area too is being revised.

A promising new application technique for reducing spray drift and soil contamination has been developed market-ready for use in viticulture while development is being continued for use in orchards. These new types of "recycling equipment" close off the treated section of the plant row in a small cubicle (very similar to a shower cubicle), thus collecting and pumping back most of those droplets that pass through the foliage without sticking to the leaves. According to data available so far, the remaining spray drift (basis value, see above) 5 m off the vineyard deposits only 0.5 % sediment while application with "standard" equipment requires 20 m distance to achieve the same level of protection of a water body. Consequently, lesser use restrictions (smaller safety distances) are prescribed for applications with recycling equipment in viticulture.

#### **12.3.1.1 Requirements**

For reducing the water contamination through spray drift use restrictions (at present NW 630-NW 636) are issued which prescribe to the user the observance of a safety distance to bodies of water. Such safety precautions must be meaningful and observable under practical conditions. For this reason the three authorities involved in authorization have established the following maximum limits for safety distances:

agriculture:                10 m  
orchards, vineyards: 20 m  
hop cultivation:         50 m  
vegetables, ornamental plants, forest: 10 m for field spraying equipment, 20 m for portable sprayers.

In individual cases (e.g. maize, aerial applications, treatment of timber staples, etc.) it is possible to deviate from these values.

#### **12.3.2 Runoff**

A generally valid model does not yet exist. Field measurements,

particularly from American "farm-pond studies" are increasingly being used for this.

Use restrictions specially for reducing contamination caused by runoff are in preparation (e.g. buffer zones of certain width and structure).

### **12.3.3 Other pathways of exposure**

Here too there still exist only isolated data, but no valid exposure model.

## **12.4 Assessment**

### **12.4.1 Course of evaluation**

- Determination of the initial concentrations to be expected in bodies of water according to currently valid exposure models (spray drift, runoff), graduated according to the crop-specifically possible and meaningful safety distances or other use restrictions.
- Estimate of the further course of concentration in the body of water, taking into consideration the concentration-reducing or elevating processes and factors (e.g. hydrolysis, microbial degradation, adsorption, photolysis or desorption, multiple application). Of particular significance here are the results of the degradation and distribution study in the water/sediment system. The time-dependent course of concentration thus determined - hereafter referred to as EEC (Estimated Environmental Concentration) - is included in the assessment of the effects.
- Selection of the most sensitive, for this substance, its properties and intended uses, biologically relevant NOEC and threshold values. Obvious "outliers" and "exotic" species are as a rule not taken into consideration. The test best simulating the real exposure pattern is given the most weight. The ERC (Ecologically Relevant Concentration) thus being established must not be exceeded as a result of the intended use.
- EECs are compared with the ERCs and the threshold concentrations (TC). Every claimed use (AWG) is viewed differentially taking into consideration the use restrictions meaningful there.
- Greatest possible (without use restrictions) EEC << ERC ==> positive assessment of this AWG.

- Greatest possible EEC close to the ERC/TC ==> change to next smaller EEC (= next greater safety distance with corresponding use restriction).
- Etc. up to the smallest EEC (= greatest possible meaningful safety distance).
- Smallest EEC close to the ERC/TC ==> defensibility decision. Depending on the data situation, mode of action, nature and scope of the effects to be expected and other information on the use, significance and effects of the product, a negative assessment of the AWG (decision depending on risk-benefit analysis) can be made even if the EEC lies below the ERC. The ecologically necessary interval between these two concentrations depends on the individual case. Rigid factors are not applied so far. Of increasing significance in this area are more extensive studies which make it possible to further pursue the effects to be procured. These include studies in model ecosystems or in the field, which in the individual case are to be coordinated between the applicant and the authorities involved in the authorization process.
- Smallest EEC > ERC ==> negative assessment of this AWG; decision depending on risk-benefit analysis.

#### **12.4.2 Decision making**

The assessment in aquatic ecotoxicology is undertaken specific all to every claimed use with complete data situation. A negative assessment of claimed uses or of the product (if all AWGs are affected) leads to a risk-benefit analysis on the department level according to the juristic standards. In case of missing but required data no assessment can be made. In these cases the product is evaluated negatively (here, cut-off criterion).

#### **12.5 Assessment of metabolites and inert ingredients**

Metabolites or co-formulants can, of course, be ecotoxicologically relevant. The more stable they themselves are, the more it is necessary to subject them to a precise examination and also to have tests or physico-chemical data worked out. The assessment standards apply correspondingly.

## **12.6 Assessment principles**

### **12.6.1 Ecological value of organisms and endpoints**

Between daphnids and fish there is no different ecological value. Both here are representative of systematic and ecological groups of animals which, where they occur, represent essential structures of the ecosystem. An assessment in the sense that only fish as so-called top members of the food chain are worth protecting is therefore rejected. The concept of the food network, i.e. a high-grade cross-linking of nearly all structures instead of a linear food chain, also includes the knowledge that many species, which because of their rarity were earlier assessed as being unimportant for the energy and matter cycles of a system, can now be given greater significance as controlling links because of certain properties. Reductions of such species through external factors can, under certain circumstances, sharply change structures and processes of the system. Prediction of this is possible only with difficulty, even for precisely known bodies of water. Overall, it is impossible within the framework of the authorization process.

In assessing effects on algae it is taken into consideration that what is involved here is not mortality, but the slowing of an otherwise exponential growth. The EC50 of the algae tests can therefore be weighted lower than, for example, the LC50 for daphnids. This does not, however, mean a general downgrading of these results, since secondary effects have to be considered.

### **12.6.2 Effects**

Incursions into natural populations have not only direct effects. The absence of a species or a retarded multiplication lead, under certain circumstances, to competition shifts and to change/interruption of food relationships. Further possible consequences in catchwords: changes in species spectrum, dominance relationships, succession sequences, energy and matter turnover, in the extreme case also gas balance of the body of water. The exact extent of such secondary effects is not predictable all-inclusively.

For direct effects such as acute mortality this naturally applies in the same manner. Added to this is the effect of suddenly dying,

sedimenting biomass that accumulates in the body of water. The following decomposition processes consume a great deal of oxygen and thus change the gas balance in particular of standing bodies of water.

Possible consequences include accelerated sapropel formation (with corresponding consequences for the hydroeconomy), change in the benthos, formation of hydrogen sulfide, oxygen deficiency in water strata near the bottom or except in the uppermost stratum with corresponding consequences for all aerobic organisms. The argument occasionally expressed in this connection that through external mortality factors only the "excess fraction" of the population present in any case is affected is not, however, acknowledged. Rather it is the state of scientific knowledge that high reproduction rates represent an adaptation to correspondingly high natural mortality rates (predation, abiotic factors), but not an excess production that can be dealt with in any way without encroaching on the basic population.

### **12.6.3 Extrapolation**

From the laboratory tests on individual species for narrowly defined life stages and functions it is necessary to extrapolate, among other things, the totality of all expressions of life, populations with non-homogeneous age structure, other species, inter-specific and intra-specific interactions and field conditions in general. Even if in some cases the formulated product is tested it is to be taken into consideration that further substance mixtures occur in the field (tank mixtures, narrow spraying sequences with active ingredient change, etc.).

The uncertainty in the prediction is all the greater the more extrapolation steps that have to be undertaken. It is not at present quantifiable. Rigid safety factors could therefore be only convention. It remains to be seen whether the use of statistical distributions brings improvements for the individual extrapolation steps (model by van Straalen and Denneman).

### **12.6.4 Persistence of effects/recovery**

Two "repair mechanisms" until the next use of the product are



conceivable: reproduction of the surviving organisms and immigration from unaffected systems. For the following reasons, however, both mechanisms cannot be all-inclusively viewed as available at any time and therefore also cannot be considered in the assessment:

Reproduction of many species is tied to spans narrowly defined by time and ecology (season, food, ...). It is successful in the sense of the population only if the offspring succeed, in reproducing. This means that the possible reproduction can be assessed as relieving only if it is assured that

- a) individuals capable of reproduction survive, and
- b) their progeny likewise survive all further applications in this crop.

This would be equivalent to the assessment (and fixing) of the entire spraying sequence, which is neither possible nor provided in the Plant Protection Act.

Immigration presupposes the existence of freely mobile stages. These frequently exist only briefly or under certain conditions. Immigration therefore cannot take place over lengthy periods. Ultimately, the immigrated individuals are subject to similar conditions (spraying sequence) as the killed population, so that a permanent recovery is at least doubtful. Especially for all species without flight-capable stages the additional objection applies that many bodies of water are so strictly divided by hydraulic engineering measures (cross-structures) that an upstream migration is impossible.

Therefore, both mechanisms do not suffice to preclude the "side effects" with "probability bordering on certainty" (paraquat decision) or to reveal their essential acceptability. Their merit in the assessment of aquatic ecotoxicology is thus considerably less than in other test areas of ecotoxicology. This can be attributed to, among other things, the essential difference that bodies of water are not target areas for the application of plant protection products.

#### **12.6.5 Field studies and model ecosystems**

Primarily, such studies will serve to examine the distribution and stability of an active ingredient in bodies of water and thus the availability for the organisms under real-life conditions. Furthermore, those compartments and organisms will be examined especially intensively that have been identified as most affected and/or sensitive. Also essential in the determination of duration and extent of the effects, since this is important information in the risk-benefit analysis. As a matter of principle, the objective is, also in field tests or model ecosystems, to examine a series of different concentrations in order to determine an NOEC of the system.

Whether the NOEC of the tested system can be converted directly as tolerable concentration into the decision, or whether a safety factor has to be inserted here depends in the individual case on the nature, duration and extent of the effects and the slope of the dose-response relationship as well as on the extent to which the tested system is representative of the bodies of water affected. Such a factor, however, can only be lower than that considered necessary on the basis of laboratory data.

#### **12.7 Criteria for use restrictions**

Regarding the use restrictions regulating the application of the product (e. g. NW 630 - NW 636; texts see BBA Guideline I, 3-5) see under 12.4.1 Evaluation.

The labelling NW 261-264 are issued by the BBA if

- EC50/LC50 < 10 mg/l (acute tests on daphnids and/or fish) or
- NOEC/LOEC < 1 mg/l (chronic or sub-chronic tests on algae, daphnids and/or fish).

NW 261: The product is toxic for fish

NW 262: The product is toxic for algae

NW 263: The product is toxic for food animals for fish

NW 264: The product is toxic for fish and food animals for fish.

## **12.8 Outlook**

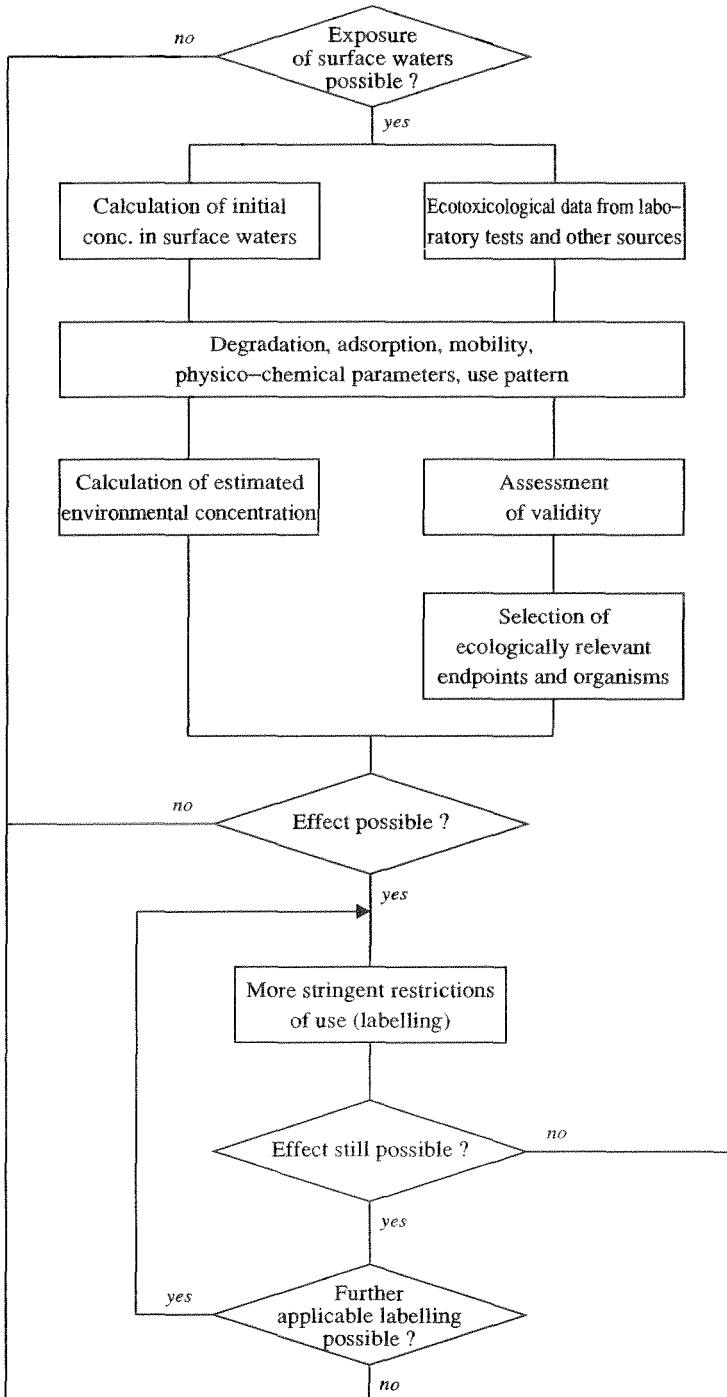
### **12.8.1 Use restrictions**

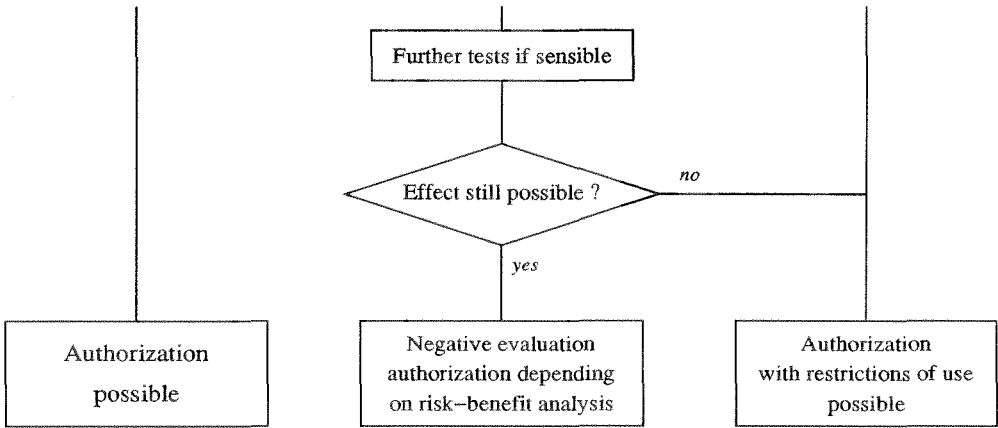
The labelling graduated according to organisms implies for many users (also consultants) also a graduated value in the sense that fish are considered more worthy of protection than that so-called "fish food-animals" or perhaps the algae. It is therefore discussed to replace the separation according to organisms by a common labelling (like: "The product is toxic for aquatic organisms"). In this way it could be avoided that with the use of plant protection products different caution would be taken depending on the value that the user affords to the organism at risk.

### **12.8.2 Test organisms**

The more stable an employed active ingredient, the more it can be accumulated by multiple application, especially in water sediments. (Stability of a product is critical especially with neutral and slightly basic pH, since most small bodies of water in agricultural areas are eutrophic and therefore exhibit such values.) Regarding the effects on the then greatly exposed benthic organisms a standardized test for sub-chronic and chronic effects under realistic exposure conditions (with sediment) is still lacking.

## 12. Side-effects on Aquatic Organisms





H. Ehle

### **13. Side-effects on soil microflora**

The soil microflora contributes considerably to maintaining soil fertility (particularly through the decomposition of plant material and plant protection products, nitrogen fixation from the air and symbiosis with plants, e. g. mycorrhiza and rhizosphere).

The studies with regard to the effects of plant protection products on the soil microflora are performed according to guideline VI, 1-1, (March 1990) of the BBA.

#### **13.1 Data requirements**

For plant protection products that are to be used on areas in the open for agriculture, horticulture or forestry, data regarding effects on activities of the soil microflora are to be submitted. Such data are not required for plant protection products, if their use is intended

- under glass or in rooms,
- for wound treatment, grafting on fruit and ornamental trees or to prevent damage caused by game,
- as spray cans in fungicidal and/or insecticidal area in the open,
- for herbicidal control of individual plants,
- on paths and open areas with tree growth,
- for the treatment of seeds, except for seed treatment of potatoes,
- against rats in the open,
- on timber/felled trees in the forest,
- as entomopathogenic micro-organisms or their metabolite products (e. g. codling-moth granulose virus, *Bacillus thuringiensis*).

The results of the studies should show whether the plant protection product to be tested has effects on activities of the soil microflora and, if so, how long negative effects (inhibitions and/or stimulations) persist. The effects on the following activities are tested:

- metabolic activity of the microbial biomass (optionally

- dehydrogenase activity, short-term respiration or metabolic activity of the biomass),
- nitrogen conversion (nitrogen mineralization and nitrification).

### **13.2 Testing**

As a rule, the tests are performed in the laboratory with the formulated product. With single application the maximum rate of application for which authorization is sought and five times that, and with multiple application the maximum rate of application and ten times that are tested.

The laboratory tests are performed with soil samples taken from two soils used for agriculture (sandy soil and loamy soil). More extensive laboratory tests and possibly glasshouse or field tests can be required. The testing modalities and the scope of the test are established between the BBA and the applicant.

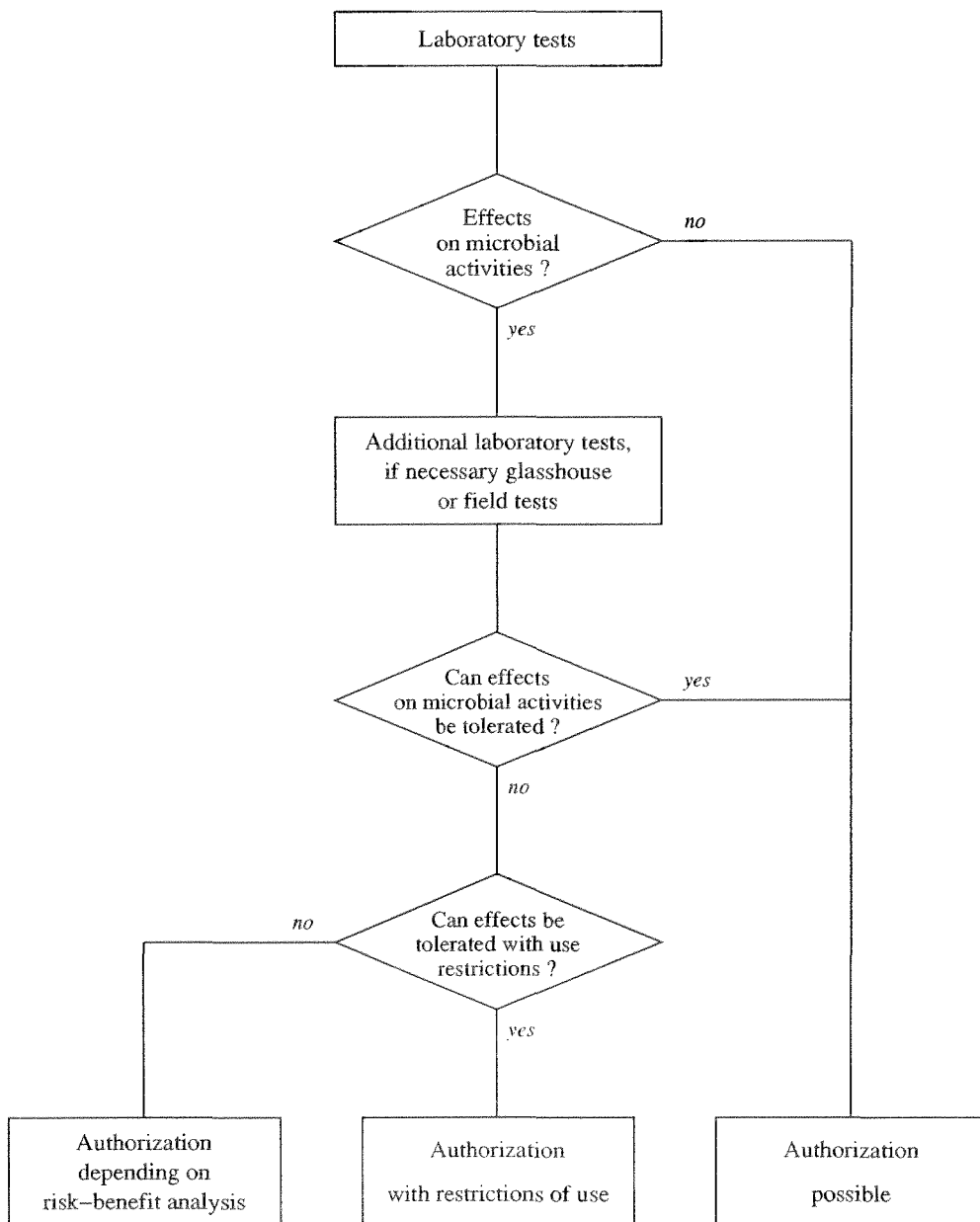
### **Assessment**

The assessment is accomplished according to the flow diagram given. The study results for a plant protection product with both rates of application in two soils are assessed equally with regard to the effects on activities of the soil microflora.

If the measurement data determined in the laboratory for activities studied have a difference smaller than  $\pm 15\%$  compared with untreated after a maximum test period of 90 days, the influence is tolerable. If the difference is greater than  $\pm 15\%$  or if the laboratory results are difficult to interpret, the performance of further laboratory tests and possibly glasshouse or field tests can be necessary. In glasshouse or field tests after a test period of a maximum of 120 days the corresponding limits for the measured data are  $\pm 25\%$  greater or less in comparison with the untreated. If the effects lie above these limits and the application modalities (e. g. repeated applications with high amounts of a product) are unfavourable for the soil microflora, this can lead to the following consequences for the plant protection product in question:

- authorization with restrictions of use,
- authorization depending on risk-benefit analysis.

### 13. Side-effects on Soil Microflora





C. Kula

#### **14. Side-Effects on earthworms**

Earthworms are important soil organisms. They contribute essentially to the aeration and mixing of the soil and play a significant role in the decomposition of organic material. Because of their different functions in the soil they were selected as test organisms in order to find out the side-effects of plant protection products on soil fauna.

The tests are used according to a stepwise testing system. The required studies are to be carried out according to the following guidelines or guideline drafts:

- OECD Guideline No. 207 (earthworm, acute toxicity tests)
- Determination of the sublethal toxicity of a substance to earthworms in an artificial soil (ISO-Draft)
- Draft for a field test with earthworms (BBA, 1991).

##### **14.1 Data requirements**

All plant protection products intended for outdoor application which can reach the soil have to be tested for possible effects on earthworms prior to authorization.

Excluded from testing requirements are e. g.:

- products for storage protection
- game repellents
- products for wound treatment and grafting
- products for use in glasshouses and closed rooms
- products for treatment of single plants only
- railroad herbicides
- products for timber treatment only
- rodenticides, if not used for large-scale treatment

In the first stage all plant protection products are to be tested according to OECD Guideline No. 207 ('Artificial soil test'). The test is carried out with the species *Eisenia foetida* with the formulated product. The aim of this test is to obtain information on the acute toxicity (LC50, 14 days). Besides this the test

provides information on the development of body weight in the course of the test. The chemical chloracetamide is used as reference substance.

In a second-stage test on reproduction in the laboratory information are obtained on the number of juveniles and the body weight development of the adults as test parameters. In this test only laboratory bred animals should be used. That is why the compost worm *Eisenia foetida* is predominantly used in the second-stage test at present. The breeding of earthworm species of cultivated areas needs a lot of time and is not possible in an adequate quantity yet. Additionally it is difficult to find out side-effects on reproduction, because of the generation period of these species.

The second-stage laboratory test is intended for cases in which the pesticide has proved to be toxic in the test on acute toxicity or if there are sublethal effects (e. g. reduction of body weight).

Pesticides which are persistent (see: behaviour of the pesticide in soil) and indicate a chronic damage of earthworms from the test of acute toxicity (dose-effect relationship) should be tested in a second-stage test. This is also valid for plant protection products with several applications. To be able to draw conclusions regarding the side-effects in the field the second-stage laboratory test has to be done with doses or concentrations relevant to practical use. In contrast to the first stage with a high safety factor only one safety factor of a five-fold applied dose is intended in the second-stage test. If effects occur with the five-fold applied dose they are assessed as impacts. A product with the active ingredient benomyl is used as reference substance.

If the results from laboratory tests are not sufficient to assess effects, field tests are required as the last test stage.

Field tests should be conducted under controlled conditions as far as possible (e. g. if necessary, also with irrigation), because earthworms are very sensitive concerning changing climatic conditions. In this way an exposure of the earthworms and an

effective sampling could be made possible. The use of a toxic standard (e. g. active ingredient benomyl) should be provided for these reasons.

In field test the side-effects of plant protection products on abundance and biomass of populations of common earthworm species have to be investigated. The duration of the test should be one year at least. Statements have to be made which describe the side-effects on the particular species.

#### **14.2 Course of the evaluation**

In order to assess effects of a plant protection product on earthworms, toxicity (determined in laboratory test) is compared with the concentration which is expected to occur initially in the field (PIEC = Predicted Initial Environmental Concentration).

The estimation of the initial concentration in soil is based on the following assumptions:

- The plant protection product is evenly distributed in the upper 2.5 cm of the soil.
- In case of low growing crops with little plant cover of the soil it is assumed that the applied dose reaches the soil in total.
- In case of low growing crops with high plant cover and in high growing crops (fruit, vine, hop) the estimated concentration is corrected according to the plant cover of the soil. In case of low growing crops the applied dose should be reduced according to the developmental stage of the crop. For high growing crops it is presently assumed that at the average 50 % of the applied dose will reach the soil surface.

If the LC50 exceeds the estimated concentration in soil by a factor of 100 the plant protection product is classified as having no or low risk for earthworms. At present a factor of 100 seems to guarantee an adequate safety for the hazard assessment - including a safety factor to transfer the results of *Eisenia foetida* to other species in arable soil.

If the LC50 is lower than the 100-fold and higher than the 10-fold estimated concentration in soil, additional criteria such as the

behaviour of the pesticide in soil, the application pattern and the application rate must help to decide whether additional laboratory tests are necessary to investigate sublethal effects in a second-stage test. It is difficult to define fixed trigger values, because additional testing depends on different factors.

If the LC50 is lower than the 10-fold estimated concentration the application of the plant protection product is assumed to involve a high potential risk for earthworms. Additional testing including field tests must show whether these effects might occur in the field.

### Assessment

Principles of risk assessment have to take into account that plant protection products are intended to be used in the habitats of earthworms. Therefore the earthworms are living in the contaminated soil during and after application.

Adult earthworms of some species have the possibility to retreat into deeper soil layers, but mobility of earthworms is very low in general. This means that reinvasion of treated areas will happen slowly. Population recovery will according to the present state of scientific knowledge therefore preferably happen by recovery of the surviving populations of the treated areas. This fact has to be considered in plant protection products which are toxic to earthworms.

To be able to assess the effects of a plant protection product on earthworms, intensity and duration of the effect are judged on in combination with the behaviour of the pesticide in soil.

If a toxicological effect is observed labelling requirements are given as general information to the applicant or as use restrictions.

Possible labelling requirements are e. g.:

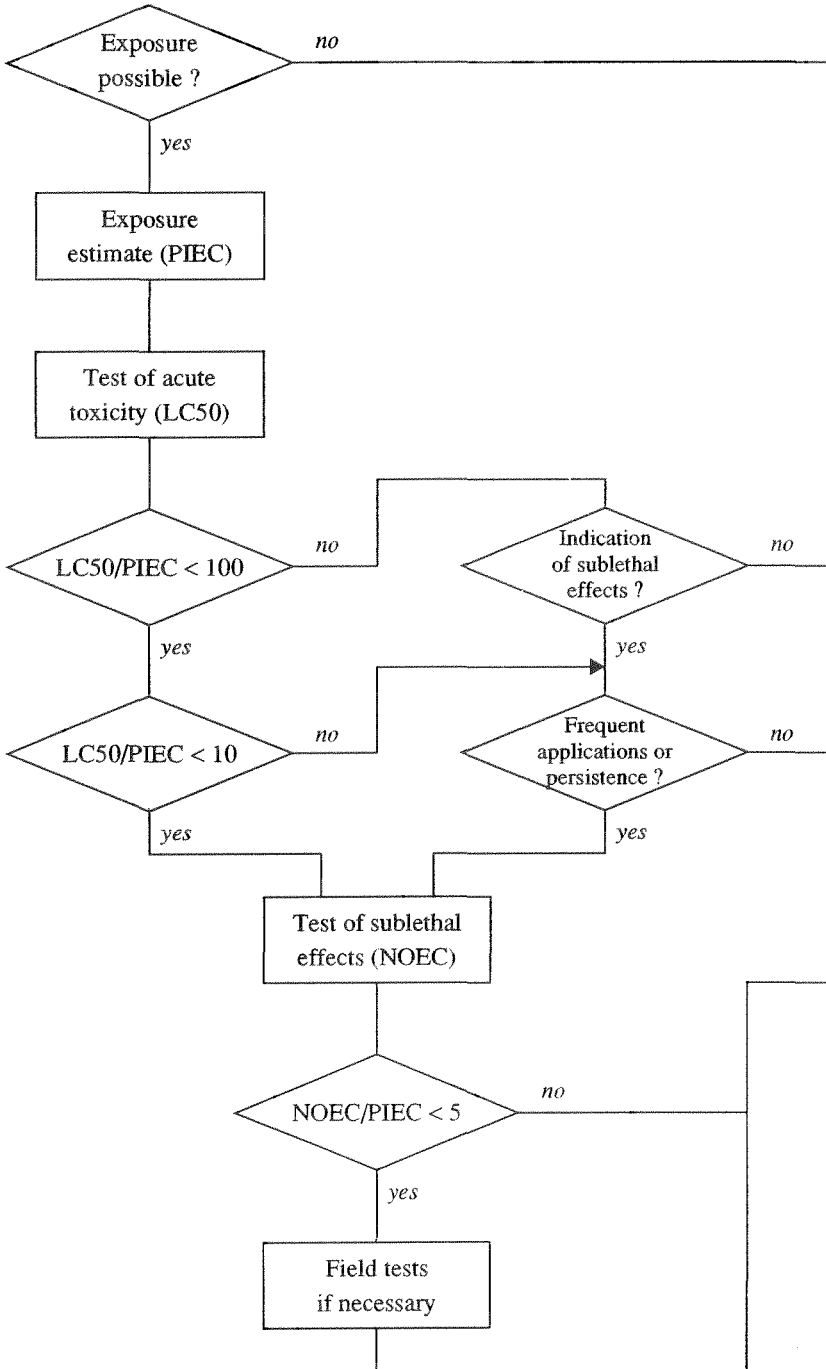
- to give general information about a possible damage to earthworm populations for a decision-aid for users and advisers (e. g. 'The plant protection product is harmful for earthworms')
- to demand for a certain time interval between treatments (e. g. 'The plant protection product including other soil fumigation

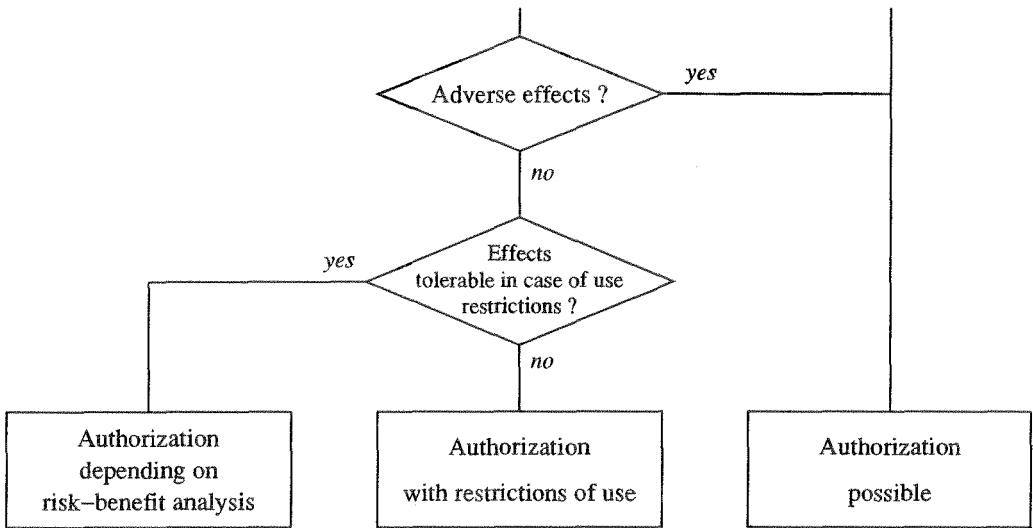
products is only to be used on the same outdoor area in intervals of two years')

- to limit the number of treatments per year

If the intended use of the plant protection product causes a damage of earthworm populations and if appropriate labelling requirements will not allow the damaged population to recover, the authorization is called in question and is depending on a risk-benefit analysis.

### 14. Side-effects on Earthworms





D. Brasse

## 15. Side-effects on bees

According to Art. 1 (2) no. 2 i of the plant protection regulations, test reports on the effects of plant protection products on bees are required as part of the authorization process. A BBA Guideline for compiling the test report is available in series VI, number 23-1. The test subject is the western honeybee (*Apis mellifera* L.).

### 15.1 Data requirements

If, under consideration of the intended use as requested for in the registration, bees are not endangered special tests are not required.

Excluded from testing requirements are e. g.:

- products for storage protection
- game repellents
- products for wound-sealing and grafting
- products for treatment of single plants only
- railroad herbicides
- products for timber treatment only
- rodenticides

The applicant can express this by the following reference to the product directions:

Because of the intended use of the product fixed by authorization bees are not endangered (B 3).

The submission of documents concerning tests conducted according to the afore-mentioned guideline is unnecessary if the applicant requests with the application for authorization that the product should be labelled "hazardous to bees" (see below, NB 661-1) and justifies this, for example, with information from tests on other test organisms.

In all other cases the testing is carried out according to the three-tiered scheme shown under 2.



## **15.2 Course of testing and assessment**

### **15.2.1 Laboratory test**

Testing includes: mortality caused by inhalation, topical application, permanent contact with fresh but dry deposit and oral uptake (feeding the test product as a sugar solution - LD<sub>50</sub>) as compared to the water control.

Bees of a healthy colony are to be used.

A precise age determination is not required. The natural mortality rate in the test, however, should not exceed 10 to 15 %. The assessment of the laboratory test is accomplished by comparison with the untreated (= water) control and the reference product hazardous to bees as the toxic standard. With regard to classification no percentages for the mortality rate are established. It is intentionally stated only that harm to the test bees in one of the 4 test forms necessitates a further testing in the next tier. This wording affords the assessor the possibility to take into consideration other forms of harm besides mortality and also to accord different weighting to the individual test forms.

If no harmful effects occur in the laboratory testing, the testing can be concluded. With the occurrence of effects the testing can be continued with the cage test (semi-field).

For the test of growth regulators (IGRs) a cage test and a field test are required even if no damage to the adult honeybees has occurred in the laboratory.

### **15.2.2 Cage test (semi-field)**

Testing includes: mortality, behavioural changes of the test bees and development of the test colony (esp. broodstatus) in comparison with water control and the reference product hazardous to bees. The testing is accomplished with twice the maximum of the recommended concentration in authorization.

If according to the results of the laboratory testing and on the basis of the mode of action of the product a classification of the product as "B 2" appears possible, the test product (PM) is

applied in the evening after the daily foraging activities of the bees until 11 p. m.,. As the reference product (VM) the respective test product is applied when bees are foraging.

As with the conversion from laboratory to cage test, no fixed numbers of damage are established in the guideline for introducing the field test.

The assessment is accomplished through the comparison of the test product with the untreated control and the reference product hazardous to bees. Not just the mortality rate, but also a possible behavioural change in the bees is included in the assessment of the test results. The assessment focuses on the question whether the development of the colony, which is regarded a segment of a population or as a minimal population, is disturbed by use of the product.

If no harmful effects occur during the cage test, the testing can be concluded. If effects occur, the testing can be continued in the field.

### **15.2.3 Field test**

Testing includes: mortality, change in behaviour of adult bees as well as development of the colony in comparison with the untreated colonies of the home apiary. Testing is done with twice the maximum of the recommended concentration for the authorization.

In contrast to the cage test, in the field test the effects of plant protection products on entire bee colonies are examined under conditions approaching actual practice. As in the cage test, the assessment of results from field test is concentrated on the question whether the development of the colony is disrupted because of the use of the product.

### **15.3 Results of the test**

If on the basis of the tests the products have proven to be "not hazardous to bees" (B 4), the applicant is afforded the possibility of including this information in the directions for the use of his product. The test results submitted must permit the

clear conclusion that the tested product does not endanger bee colonies when applied to flowering plants. It should be noted here that products with a certain toxicity not absolutely have to endanger bee colonies when applied in practice.

Labelling as "not hazardous to bees" is always tied to the maximum recommended rate for application in plant protection.

Preparations with known active ingredients that in many tests have proven to be not hazardous for bees can on the basis of this information also be classified as not hazardous to bees without renewed testing.

If, however, on the basis of the test results submitted the products have proven to be hazardous to bees, labelling requirements for the instructions for use will be issued. The following requirements are possible:

1. **NB 661-1:** The product is classified as hazardous to bees (B 1).  
The product may not be used on flowering crops or those encountered by bees. Note bee protection regulations of 22 July 1992.

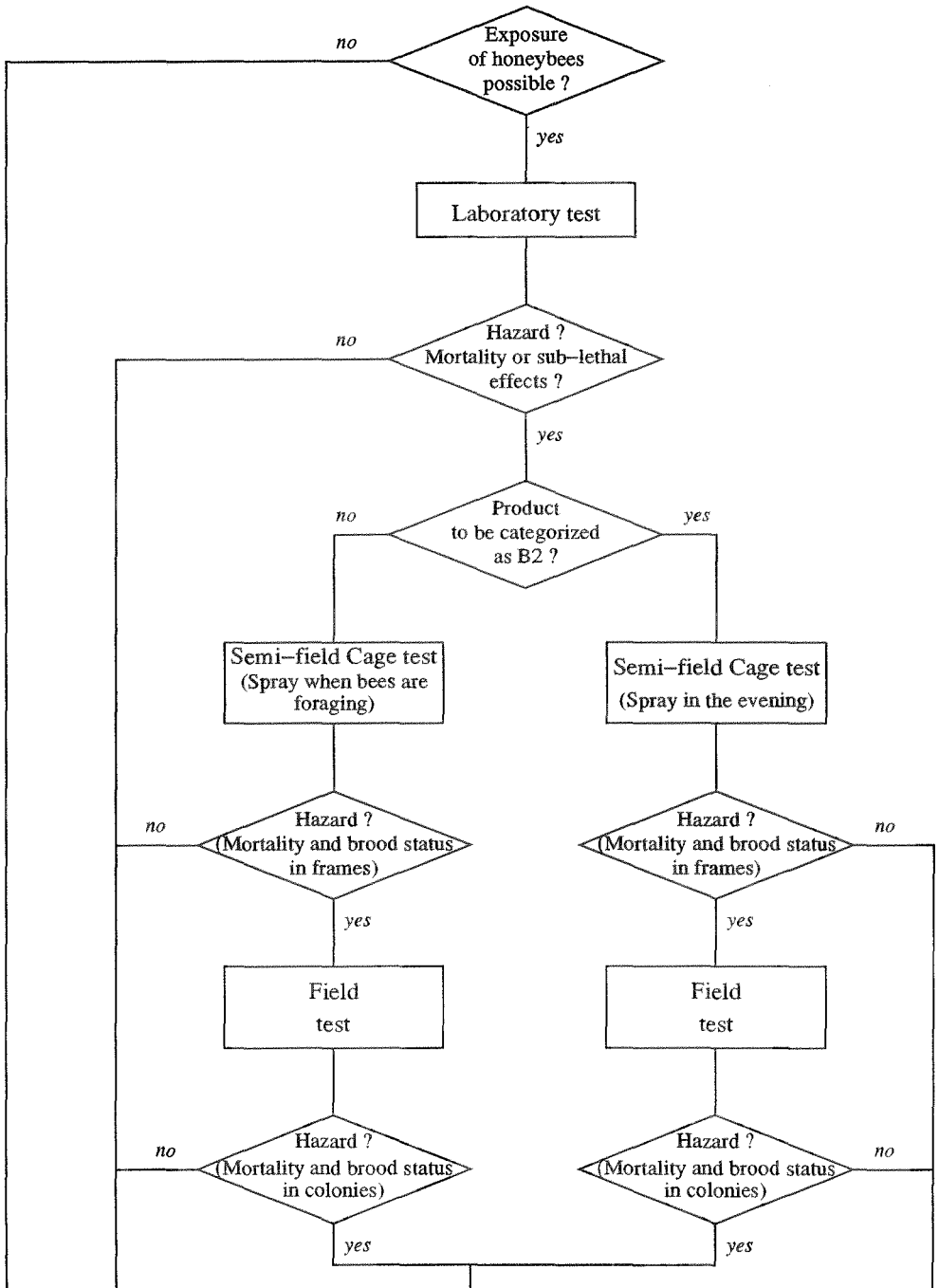
This requirement is also issued if requested by the applicant with the application for authorization, and if it is adequately justified.

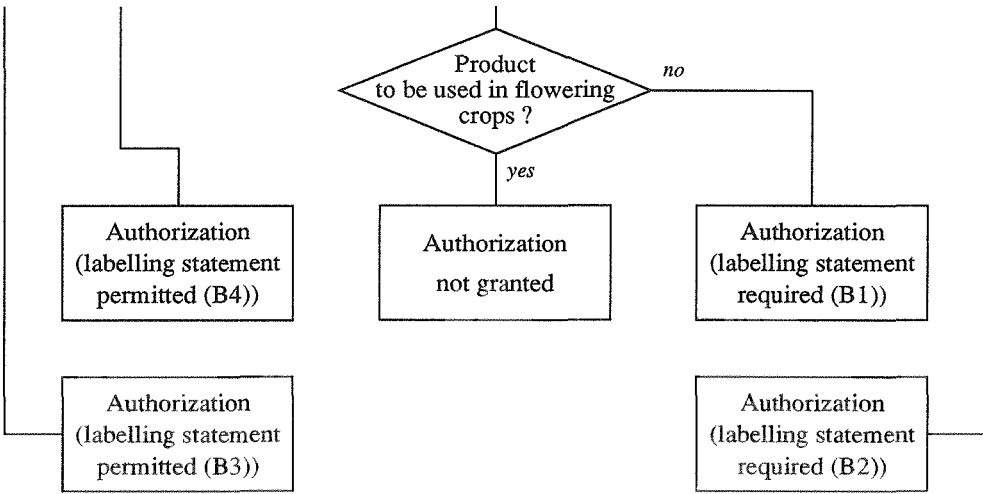
2. **NB 662-1:** The product is classified as hazardous to bees except when used after the end of foraging activities in the evening up to 11 p. m. (B 2). The product may not be used on flowering crops or those encountered by bees except during this period of time. Note bee protection regulation of 22 July 1992.

It must be demonstrated through tests that take into account the special mode of application of these products that no harm to bees can occur after authorized and proper application.

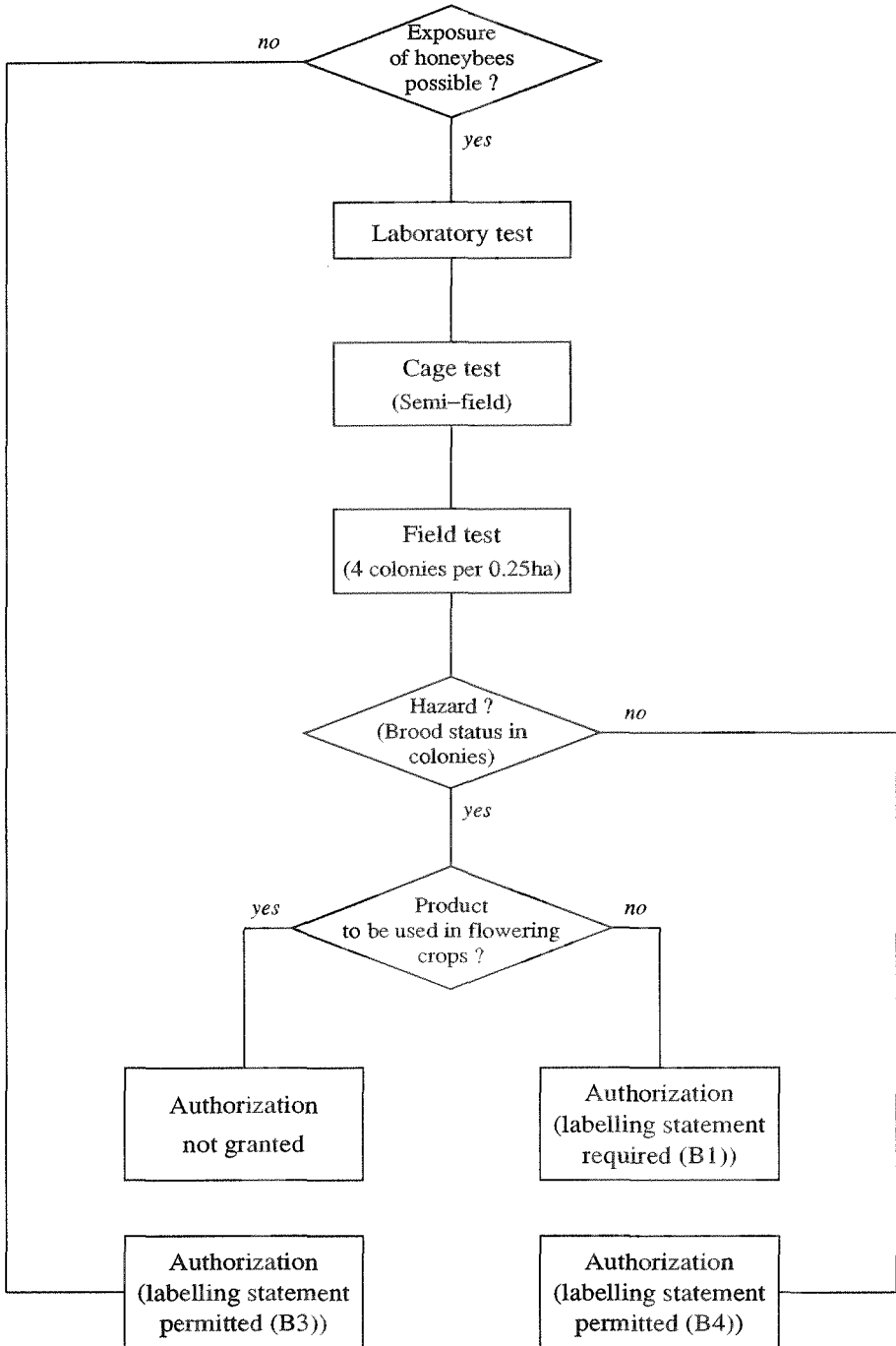
The refusal of an authorization of a plant protection product is considered only if it is classified as hazardous to bees (B 1) and the intended use of the product makes the application in flowering crops necessary.

15a. Side-effects on Honeybees (IGRs not considered)





15b. Side-effects on Honeybees (IGRs)



D. Brasse, H. Rothert

## **16. Side-effects on beneficial organisms**

According to Art. 1 (2) no. 2 j of the plant protection regulations test reports concerning the effects of plant protection products on several beneficial arthropods other than bees are required, as part of the authorization procedure. [Note: The term "beneficial arthropods" in the aforementioned regulations will have to be replaced by the term "beneficial organisms".] Available for compiling the test reports are various BBA guidelines of series VI as well as numerous test methods of the International Organization for Biological Control (IOBC).

### **16.1 Data requirements**

If under consideration of the intended use as requested for in the authorization beneficial organisms are not endangered, special tests are not required.

Excluded from testing requirements are e. g.:

- products for storage protection
- game repellents
- products for wound-sealing and grafting
- products for treatment of single plants only
- railroad herbicides
- products for timber treatment only
- rodenticides

The applicant can express this with a reference worded:

Because of the intended use of the product fixed by the authorization, populations of relevant beneficial organisms are not endangered.

The submission of documents concerning tests performed in accordance with guidelines is also unnecessary if with the application for authorization the applicant requests that the product be labelled as "hazardous" with regard to beneficial organisms, and justifies this, e. g. with information from other tests or also screening tests.

In all other cases the testing is accomplished as a rule according to the three-tiered plan shown under 16.2.

## **16.2 Course of testing and assessment**

### **16.2.1 Laboratory test**

Testing includes: Mortality and reduction of beneficial capacity (feeding capacity of predators, parasitization capacity of parasites), fertility, as compared to the water control.

The assessment of the data is accomplished according to the directions of the corresponding guidelines. At present, assessment of the test results is done on the basis of the assessment schemes devised by the IOBC working group "Pesticides and Beneficial Organisms" (= International Organization for Biological Control).

#### Assessment scheme for laboratory tests:

W 1 = harmless	< 30 %	Reduction of beneficial capacity or mortality
W 2 = slightly harmful	31-80 %	Reduction of beneficial capacity or mortality
W 3 = moderately harmful	81-99 %	Reduction of beneficial capacity or mortality
W 4 = very harmful	> 99 %	Reduction of beneficial capacity or mortality

If no harmful effects for the test organism occur in the laboratory testing, the testing can be concluded. If hazards to the test organism occur, the testing can be continued in semi-field tests. If no suitable test methods are available for semi-field tests, either a field testing may follow, or a negative labelling statement referring to the respective species tested in the laboratory must be issued (see under 16.3).

### **16.2.2 Semi-field test**

Testing includes: Mortality and reduction of beneficial capacity (reduction of feeding capacity of predators, reduction of parasitization capacity of parasites), fertility, as compared to the water control.



The assessment of the documents is accomplished according to the directions of the corresponding guidelines. At present, the assessment of the test results considers four classes according to the assessment schemes devised by the IOBC working group "Pesticides and Beneficial Organisms" (= International Organization for Biological Control).

Assessment scheme for semi-field and field tests:

W 1 = harmless	< 25 %	Mortality or beneficial capacity
W 2 = slightly harmful	25-50 %	Mortality or beneficial capacity
W 3 = moderately harmful	51-75 %	Mortality or beneficial capacity
W 4 = very harmful	> 75 %	Mortality or beneficial capacity

If the product proves to be harmless for the test organism in the semi-field test, the testing can be concluded. If corresponding test methods are available, and increasing mortality or reduction of beneficial capacity or fertility had to be stated the testing can be continued in the field. If in these cases the testing is not continued, the product is provided with a negative labelling statement with reference to the species tested (see under 16.3).

**16.2.3 Field test**

Field tests are complicated, time consuming, expensive and difficult to reproduce. Also single-species tests are possible only in a few cases. For this reason field tests mostly are planned as ecological field studies (multi-species tests).

**16.3 Results of the test**

The question of the concluding classification of the products with regard to their effect on beneficial organisms is still not satisfactorily solved, since for most test organisms there are only laboratory tests, and only for a few organisms semi-field and field tests are available.

From the approach described above it can be seen that the products

as a rule can be conclusively evaluated only if no harmful effects have been detected in the laboratory or semi-field test. Within the course of a laboratory test it is possible to prove only the toxicity of a product for a test organism. It can be concluded from this that with regard to their effect on beneficial organisms numerous products cannot be conclusively assessed, since a toxicity found in the laboratory may not result in hazardous impacts on beneficial organisms when the product is used in practice. At present there are still little data on the correlation of results derived from the laboratory test and the field test.

Nevertheless, the available data must be converted into a labelling statement. For this, the procedure is as follows:

If on the basis of laboratory testing the products have proven to be not toxic for the respective species tested, or non-hazardous on the basis of more extensive testing, the applicant is afforded the possibility of including this as information in the directions for the use of this product. The text contains the following wording:

The product is classified as harmless for populations of ... (respective species tested).

If, however, on the basis of the data submitted it has been found that a hazard is to be expected, depending on the severeness of the hazard two different labelling statements are possible:

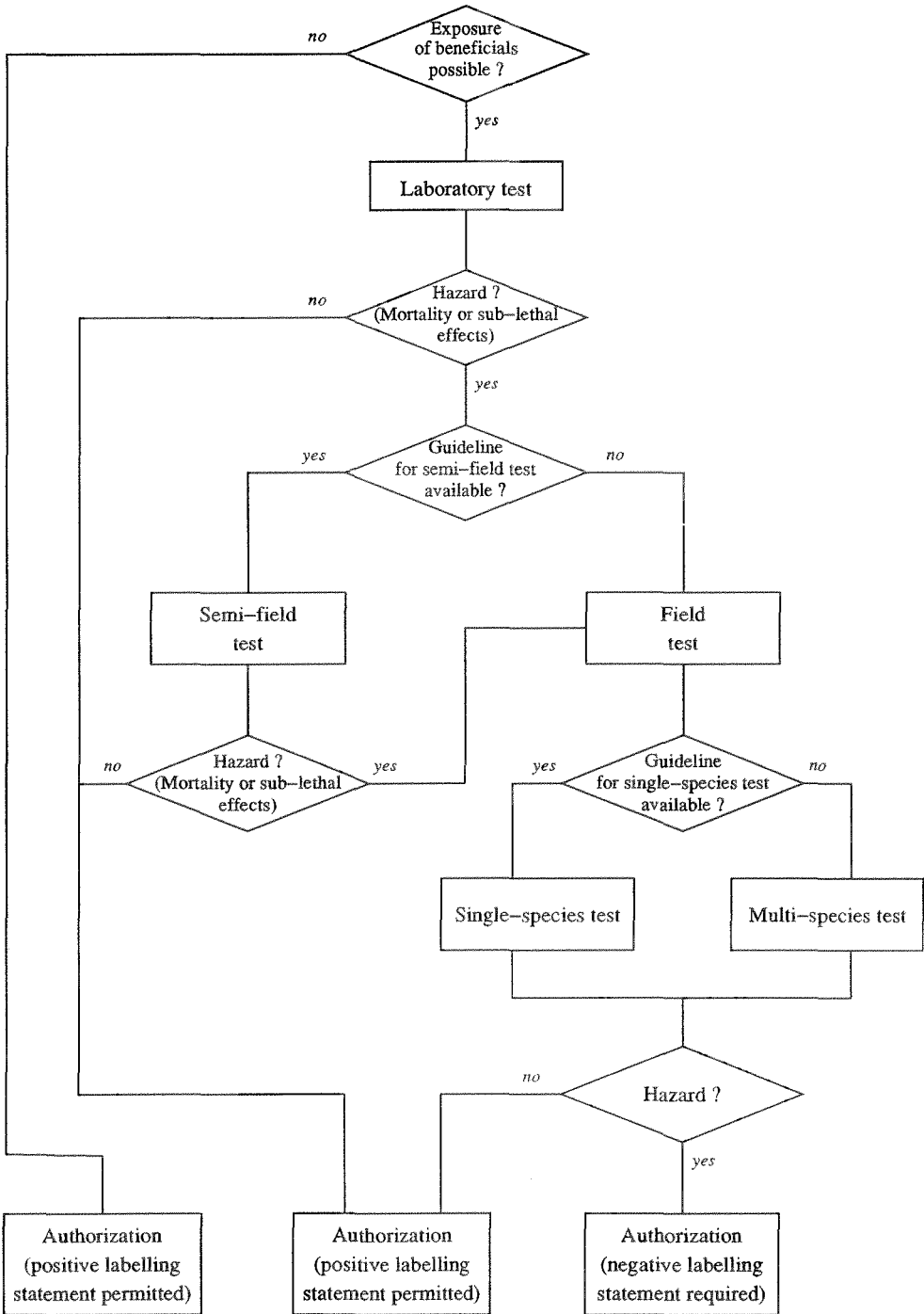
The product is classified as moderately harmful for populations of ... (respective species tested).

The product is classified as harmful for populations of ... (respective species tested).

For these classifications it is still being examined how the assessment steps of the IOBC can be converted. The assessment for classification of the effects of products in *Typhlodromus pyri* in viticulture can be found in the BBA Guideline VI 23 - 2.3.4. The wording of the statements NN 604, NN 605 and NN 606 cited there will be incorporated into the aforementioned general scheme.

Predominantly labelling statements will be assigned that refer to the respective species tested. The refusal of an authorization as a rule does not arise from the results of the beneficial organisms testing alone.

### 16. Side-effects on Beneficial Organisms



G. Joermann

## **17. Side-effects on birds and free-living mammals**

The assessment of this aspect extends to all wild bird and mammal species. The testing is not necessary if any exposure of birds and mammals is precluded; normally this applies for applications in greenhouses and in rooms.

The required studies are to be conducted according to the following guidelines:

- BBA Guideline VI, 25-1: Guideline for testing of plant protection products for hazards to birds - Acceptance tests.
- OECD Guideline 205: Avian dietary toxicity test.
- OECD Guideline 206: Avian reproduction test.

### **17.1 Data requirements**

#### a) Mammals

The basic information is constituted by toxicity data on laboratory animals generated for the evaluation of human safety. Since the transfer to other species, especially those of other orders, is affected by uncertainties, in exceptional cases additional toxicity studies with wild animals can become necessary.

Further toxicity tests may become necessary in certain cases, e. g. for secondary hazards of rodenticides if this risk cannot be estimated through model calculations.

#### b) Birds

The basic data consist of the acute oral toxicity of the active ingredient for two bird species. A smaller test scope is to be justified. The Japanese quail and another species should be selected; the bobwhite can be tested in the place of the Japanese quail. A data file in accordance with the EPA requirements (acute toxicity in one species, 5-day feeding test in two species) can also be accepted.

The acute toxicity of the formulated product is estimated in first approximation according to the active ingredient content and, for products containing more than one active ingredient, assuming an additive effect. If such an estimate is not possible because effects by inerts or synergistic effects are to be expected, and if on the basis of the remaining data a risk for birds cannot be precluded, the acute oral toxicity of the product is to be determined in one bird species experimentally.

In the case of seed treatment products, baits and granular material data on the amount of active ingredient in a certain number of seeds or particles are required, and with granular material additionally data on the distribution of particle size. An acceptance test according to BBA Guideline VI, 25-1 is to be conducted with granules if the LD50 (mg/kg) is contained in less than 4000 particles of the main size class (thus < 100 particles for a bird weighing 25 g), or the lethal threshold dose (mg/kg) in less than 1000 particles (thus < 25 particles for a 25-g bird), and with treated seed if its exclusive consumption by birds can cause toxic effects.

In the case of baits an acceptance test is required only if actual uncertainties exist concerning the attractiveness, e. g. with molluscicides; for rodenticides this test is usually not useful.

In particular cases additional studies can become necessary, e. g.

- on the hazard of secondary poisoning, if this risk cannot be estimated by model calculations;
- on reproduction toxicity, if birds, because of the intended use pattern (type and frequency of applications), are expected to be continuously exposed during the reproduction period, or if the active ingredient is persistent and has a bioaccumulation potential, so that a long-term contamination of food can occur;
- determination of residues in food;
- field tests, if the laboratory data on toxicity in conjunction with the exposure estimate are not sufficient for an assessment.

## **17.2 Course of the evaluation**

For estimating possible effects of a plant protection product on birds and free-living mammals the exposure to be expected is compared with the toxicity.

### **a) Acute hazard**

The maximum intake of the active ingredient to be expected per day is to be compared with the acute oral toxicity (unit: mg/kg body weight) or the short-term residue in the feed to be expected with the results of the 5-day feeding test (unit: mg/kg feed). The basis of the exposure estimate is the concentration of the active ingredient in available items or products. This information is immediately available for granular material, baits, and treated seeds. With spray applications the initial concentration in feed plants and invertebrates is derived as far as possible from actual residue measurements, otherwise estimated on the basis of empirical data (Kenaga EE, 1973: Factors to be considered in the evaluation of the toxicity of pesticides to birds in their environment. Environmental Quality and Safety II, New York, pp. 166-181). Further factors in the exposure estimate are the fraction that the contaminated material has in the total amount of feed of the relevant animals and the daily feed demand in relation to body weight.

As a rule the most sensitive bird or mammal species is used for the exposure-toxicity comparison. LD50 and lethal threshold dose, resp. LC50 and lethal threshold concentration are taken for the first rating of the product to be assessed. In the final evaluation, however, sublethal effects are also to be taken into consideration, and the assessment is to be based on the actually safe dose.

The hazard of poisoning by inhalation or contact is also estimated by comparing exposure and toxicity. However, present methods or models do not enable a satisfactory estimation of the exposure of free-living animals to contaminants via these routes.

b) Chronic hazard

The expected long-term residue in the feed is compared with the NOEL of the (sub)chronic or reproduction toxicity (unit: mg/kg feed).

**Assessment**

If from the ratio of exposure and toxicity it is concluded that a hazard exists for birds or mammals, it is examined whether the exposure can be precluded or reduced by posing restrictions on the use or by requiring safety precautions on the label. Cited below for several possible labelling requirements are the conditions under which they are issued.

Labelling	Condition
Collect remaining bait at the conclusion of the control operation.	If rodenticide baits are intended for placing at defined bait sites.
Not to be applied on areas free of vegetation in order to prevent uptake by game and birds.	If rodenticide baits are intended for an open and large-scale application.
Do not place baits uncovered.	For all rodenticides unless access for non-target species is prevented otherwise.
Remove dead rats and mice during and after rodent control operation.	If dead rodents can be met by predators and the active ingredient can cause secondary poisoning.
Work granules carefully into soil or cover with soil.	If in acceptance tests mortalities occurred or fewer than 10 particles are lethal for a bird.

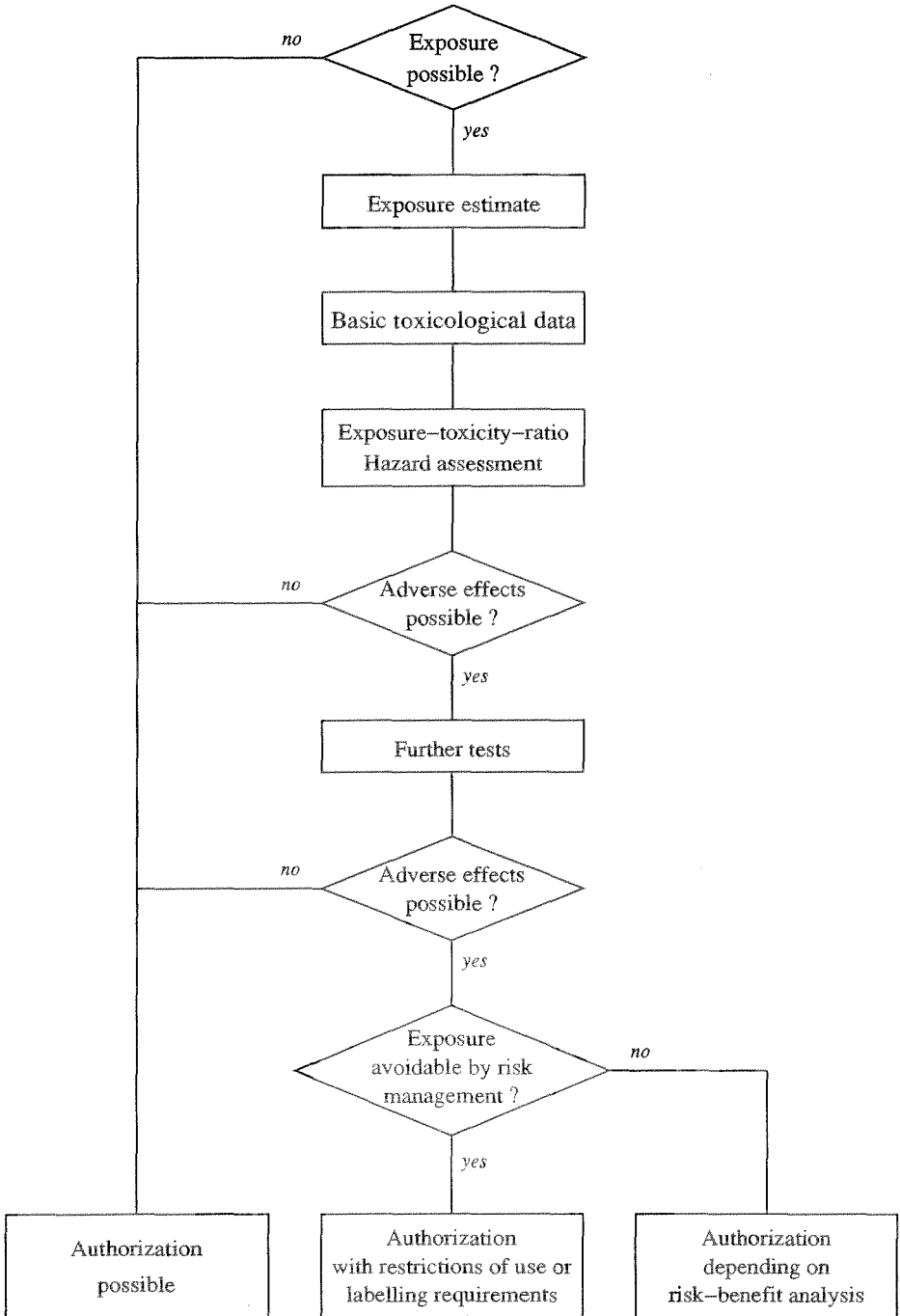


In vegetables tending to form puddles on the leaves spray applications only up to the 16-leaf-stage.

If the LD50 (mg/kg) is contained in less than 10 ml spray liquid (=2.5 ml for a 25-g bird); the calculation is based on the dosage applied to plants up to a height of 50 cm and on 600 l water per ha.

The evaluation in this scheme results in negative if it cannot be prevented through restrictions of use or labelling requirements that birds or mammals with the intended application of the product will be harmed or restricted in their ability to survive or reproduce. In this case the authorization is called in question and is depending on a risk-benefit analysis.

### 17. Side-effects on Terrestrial Vertebrates



Federal Health Office (BGA)

**18. Principles for health assessment of plant protection products in the authorization procedure**

**Toxicology**

**18.1 Introduction**

To be taken as a basis for the health assessment of plant protection products is the intention of the Plant Protection Act, according to which the authorization certificate for a plant protection product is to be granted, when it is used for its intended purpose and in the correct manner, or as a result of such use a) it does not have any harmful effects on human or animal health or on ground water, and b) does not have any other effects, particularly with regard to the natural balance, which are not justifiable in the light of the present state of scientific knowledge (Article 15, para 1, No. 3 Plant Protection Act).

The health assessment of plant protection products is accomplished fundamentally according to scientifically recognized rules and principles that are also applied internationally. In special cases, however, this does not preclude that an authorization certificate will be denied (or granted) although in other countries an authorization certificate exists (or does not exist). A plant protection product, with great probability, has no harmful health effects if there is an adequate margin of safety between the possible exposure and the dose without or with effect. The level of the safety factor is determined by the severity of the effects found in the toxicological investigations.

To the extent that the toxicological studies with the active ingredient or the commercial preparation indicate hazard potentials, according to the provisions of the Hazardous Materials Regulations, the product is to be labeled with corresponding warning symbols, comments to special dangers (R clauses) and with safety suggestions (S clauses). The hazard labeling encompasses acute effects and long-term effects of the plant protection product and the active ingredient, respectively, regardless of whether these effects are to be attributed to a single or repeated or lengthy exposure. According to the Hazardous Materials

Regulations it is the purpose of the classification and labeling to provide the public and those persons who handle these substances and preparations essential information on their hazardous properties and possibilities for avoiding dangers. The labelling takes into consideration dangers that can occur with customary handling and use of hazardous substances and preparations. The information refers to substances and preparations such as are marketed, but not to the form in which they can be used (e. g. diluted) (Hazardous Materials Regulation, Annex I, No. 1.1.1.2).

The labeling of plant protection products is prescribed by the Federal Health Office. In addition, the necessary, more far-reaching conditions for the protection of the user for inclusion in the instructions for use are also provided. The protective conditions are adapted to the specific requirements in the individual use situations.

Essentially, the agreement to authorization is granted only for such plant protection products that can be handled and spread with reasonable personal protective equipment for the respective planned application area. An agreement to authorization is not granted if indications from test documents or other empirical reports are available indicating the product or the active ingredients or inert ingredients as a considerable, uncontrollable health hazard with customary handling and storage, but also with unintended exposure (e. g. as a result of negligence).

Additional general principles in the health assessment of plant protection products in the registration process are presented and briefly explained below.

### **18.2 Acute toxicity/irritant effect**

The basis for assessment are animal-experiment tests for acute toxicity after oral, dermal and inhalative giving, tests for skin and eye irritation and for sensitizing. If appropriate, practical experiences regarding the effects on humans will also be applied. Results from testing procedures developed as alternatives to animal experiments are taken into consideration if the tests have

been performed according to internationally recognized scientific methods.

As a rule, no agreement to authorization will be granted for plant protection products that a) lead to death or to severe health damage despite immediate therapeutic measures, or b) that lead to severe skin or eye damage with single, short-term contact despite immediate therapeutic measures, or c) lead to severe allergic reactions in a considerable number of persons or if, on the basis of other studies, these reactions are to be expected with great probability. This means that even with foreseeable mistakes, e. g. non-observance of simple safety measures (wearing of protective gloves or protective goggles), an irreversible health impairment may not occur.

### 18.3 Toxicity with repeated or lengthy exposure

The basis for assessment are animal-experiment tests for subcutaneous, subchronic and chronic toxicity as well as for toxicokinetic and biotransformation properties. If appropriate, further special studies are to be included, e. g. in order to assess possible neurotoxic or immunotoxic properties.

Plant protection products for which with repeated or lengthy uptake no adequate safety factor between exposure and the hazardous dose exists will not be authorized.

### 18.4 Carcinogenic properties

The basis for assessment are long-term carcinogenicity studies on mammals, short-term tests for carcinogenic and mutagenic properties and, if appropriate, epidemiological studies.

For substances with carcinogenic properties there is no internationally uniform regulation regarding their authorization as plant protection products. This is especially true for the assessment of substances that in animal experiments have led to an increased rate of neoplasms.

In the EC, with the current state of information, substances with carcinogenic properties are divided into three categories

(according to Guideline 91/325/EEC):

Category 1: Substances that are known to have a carcinogenic effect in humans. Sufficient evidence is available for a causal relationship between the exposure of a human to the substance and the development of cancer.

Category 2: Substances that should be regarded as carcinogenic for humans. There is adequate evidence for the justified assumption that the exposure of a human to the substance can produce cancer. This assumption is generally based on the following:

- suitable long-term animal experiments,
- other relevant information.

Category 3: Substances that because of possible carcinogenic effect in humans give cause for concern, but concerning which insufficient information is available for a satisfactory assessment. From suitable animal experiments there is some evidence which, however, is not sufficient for classifying a substance in category 2.

The inclusion of a substance in Category 1 is accomplished on the basis of epidemiological data. Inclusion in Categories 2 and 3 is based primarily on animal experiments.

For classification of a carcinogenic substance of Category 2 either positive results for two animal species or a definitely positive proof for one animal species and supporting indications such as genotoxicity studies, metabolic or biochemical studies, triggering of benign tumors, structural relationships to other known carcinogenic substances or data from epidemiological studies that suggest a connection should be available.

Category 3 currently comprises two sub-groups:

- a) Substances that have been well studied, but for which the demonstration of a tumor-triggering effect is not sufficient to classify them in Category 2. No further information relevant for the classification is expected from additional tests.

- b) Substances that have not been adequately investigated. The available data are inadequate, but they give cause for concern for humans. This classification is provisional. Further studies are necessary for a final decision.

Important for distinguishing between Categories 2 und 3 are the following arguments which reduce the significance of the experimental tumor-triggering with regard to a possible exposure of humans. In most cases these arguments, especially in combination, would lead to a classification in Category 3, even if tumors were triggered in animals:

- Carcinogenic effects only in very high doses that exceed the "maximum tolerated dose." The maximum tolerated dose is characterized by toxic effects that do not yet reduce the life expectancy, but which are accompanied by physical changes such as a reduction by about 10 % in the body weight increase.
- Occurrence of tumors, especially from high doses, only in special organs of certain species, of which it is known that they have a tendency toward a high spontaneous tumor formation.
- Occurrence of tumors only at the site of application in very sensitive test systems (e. g. i.p. or s.c. giving of certain locally effective compounds), if the respective target organ is not relevant for humans.
- No genotoxicity in short-term tests in vivo or in vitro.
- Presence of a secondary effect mechanism from which a threshold value can be derived (e. g. hormonal effects on target organs or on physiological regulation mechanisms, chronic stimulation of cell growth).
- Existence of a species-specific mechanism of tumor formation (e. g. via specific metabolic paths) that is of no significance for humans.

The following arguments, in which cause for concern for humans is precluded, apply to distinguishing between Category 3 and no classification:

- A substance should not be classified in any of the categories if the mechanism of tumor formation has definitely been determined in a test and it has been demonstrated that it cannot be extrapolated to humans.

- If there are only data on liver tumors in certain especially sensitive strains of mice with no other additional evidence, the substance is not classified in any of the categories.
- Special attention should be given to cases in which only tumor data on neoplasias at localizations and in strains in which they are known to occur at a high spontaneous rate are available.

For plant protection products that contain an active ingredient classified in Category 1 no agreement for authorization will be granted. For plant protection products that contain an active ingredient classified in Category 2, as a rule no agreement for authorization will be granted.

In exceptional cases the agreement with an authorization can be granted for substances of Category 2 if for these active ingredients a great benefit is demonstrated and replacement substances with less critical properties are not available, and if the quantitative risk assessment shows a negligibly additional risk of cancer. As a rule, to be used here as the strictest calculation model is a linear extrapolation (or also the "multi-stage model"). If a risk of less than  $1:10^6$  results, with exposure the additional risk of cancer to be expected probably lies in the same order of magnitude as that of a large number of other substances contained in food or present in the environment. Also in the USA the apparently acceptable additional risk of cancer through plant protection products is given as  $1:10^6$  to  $1:10^5$  with life-long exposure. The corresponding dose is referred to as "virtually safe dose." Accordingly, plant protection products or active ingredients with carcinogenic and genotoxic properties can in exceptional cases also be authorized if the life-long exposure of user and consumer lies below the "virtually safe dose," and no detectable residues occur in foodstuffs.

### **18.5 Mutagenic properties**

The basis for assessment are animal-experiment studies in mammals, invitro tests on mammal cells and microorganisms and possibly epidemiological studies.



In the EC, with the present state of knowledge, substances with mutagenic properties are divided into three categories (according to Guideline 91/325/EEC):

Category 1: Substances that are known to have a mutagenic effect in humans. There is sufficient evidence for a causal relationship between the exposure of a human to the substance and inheritable damage.

Category 2: Substances that should be regarded as mutagenic for humans. Sufficient evidence exists for the justified assumption that exposure of a human to the substance can lead to inheritable damage. This assumption is generally based on the following:

- suitable animal experiments,
- other relevant information.

Category 3: Substance that give cause for concern because of possible mutagenic effects on humans. From suitable mutagenicity tests some evidence is available, but it is not sufficient to classify the substance in Category 2.

In order to include a substance in Category 1 sufficient evidence from epidemiological studies on mutations in humans is required. Examples of such substances are as yet not known. It is admitted that it is extraordinarily difficult to obtain reliable information from studies of the frequency of mutations in human populations or of the increase in frequency.

Necessary for classifying a substance in Category 2 are positive results of studies that can demonstrate the following:

- a) mutagenic effects or
- b) other cellular interactions, relevant to mutagenicity, in germ cells of mammals in vivo, or
- c) mutagenic effects in somatic cells of mammals in vivo together with sufficient evidence that the substance or a relevant metabolite reaches the germ cells.

The following processes are currently suitable for classification in

Category 2:

2a) Mutagenicity test on germ cells in vivo:

- test for specific locus mutation,
- test for inheritable translocation,
- test for dominant-lethal mutation.

These test systems show whether the offspring is affected or whether a defect occurs in the developing embryo;

2b) In-vivo investigations that show relevant interactions with germ cells, as a rule DNA:

- studies of chromosomal abnormalities as determined in cytogenetic analyses, including aneuploidies caused by malsegregation of chromosomes,
- test for sister-chromatid exchanges (SCE),
- test for unscheduled DNA synthesis (UDS),
- studies of (covalent) bonds of the mutagenic substance to the germ cells DNA,
- studies of other types of DNA damage.

These studies provide more or less indirect evidence. Positive results in these studies as a rule are supported by positive results from in-vivo mutagenicity studies of somatic cells of mammals or humans (see also Category 3, preferred procedures as under 3a).

2c) In-vivo studies, which show the mutagenic effects on somatic cells of mammals (see 3a), in conjunction with toxicokinetic or other processes with which it can be shown that the substance or a relevant metabolite reaches the germ cells.

Positive results from host-mediated-assay tests or the demonstration of undoubted effects in in-vitro studies can be used to support the results according to 2b and 2c.

In order to include a substance in Category 3 it is necessary to have positive results from studies with which

- a) mutagenic effects or
- b) other cellular interactions, significant for the mutagenicity, in somatic cells of mammals in vivo can be demonstrated. Especially the latter are as a rule supported by positive results from in-vitro mutagenicity studies.

The following procedures are currently suitable for the detection of effects in vivo:

3a) mutagenicity studies in vivo:

- micronucleus test or bone marrow or metaphase analysis,
- metaphase analysis on peripheral lymphocytes,
- mouse coat colour spot test.

3b) Studies of DNA interactions in vivo:

- test for sister-chromatid-exchange (SCE) in somatic cells,
- test for unscheduled DNA synthesis (UDS) in somatic cells,
- studies of DNA damage, e. g. alkaline elution, in somatic cells.

Substances that yield positive results only in one or several in vitro mutagenicity tests should as a rule not be classified. However, further studies by in vivo investigations are absolutely called for. In exceptional cases, e. g. in the case of a compound that yields distinct effects in several in vitro investigations for which no relevant in vivo data are available and which exhibits similarities with known mutagenic or carcinogenic substances, a classification in Category 3 can be considered.

As a rule, no agreement for authorization will be granted for plant protection products that contain a substance classified in Category 1 or 2.

### **18.6 Embryo-/Fetotoxic properties**

The basis for assessment are animal-experiment studies in mammals (multigeneration and segment studies), epidemiological studies and possibly in vitro studies.

In the EC, with the current state of knowledge, substances with reproduction-toxic properties are divided into two categories (however, a division into three categories is planned for the future) (according to Guideline 91/325/EEC):

Category 1: Substance that are known to have a embryo-/fetotoxic effect in humans. Sufficient evidence is available for a causal

relationship between the exposure of a human to the substance and non-hereditary maleformation of the direct progeny.

Category 2: Substances that should be regarded as embryo-/fetotoxic for humans. There is sufficient evidence for the justified assumption that the exposure of a human to the substance can lead to non-hereditary maleformation of the direct progeny. This assumption is generally based on the following:

- suitable animal experiments,
- other relevant information.

In assigning substances to these categories it is necessary to observe the criteria listed by the DFG (Deutsche Forschungsgemeinschaft) and customarily applied internationally in order to prevent an unjustified classification and labelling.

In order to assign a substance to Category 1 unambiguous epidemiological findings must be available. As a matter of principle, agreement for authorization is not granted for plant protection products that contain an active ingredient classified in Category 1.

In order to assign a substances to Category 2 unambiguous results from suitable animal experiments must be available that show that the oral, dermal or inhalative exposure of a mammal can cause a lasting disruption of the fetal development in the dam or a lasting impairment of the postnatal development of the offspring which cannot be classified as a maternal-toxic effect. The amounts administered should, taking into consideration an adequate safety factor, correspond to the possible exposure of humans. In the view of the Federal Health Office the classification of a substance in Category 2 requires a labelling of the plant protection product if the active ingredient content of the commercial preparation is so high that a not-negligible risk exists for the user or the consumer. The potential risk is estimated with the aid of safety factors (or possibly suitable extrapolation models) and taking as a basis realistic exposure possibilities, including foreseeable, inadvertent exposures. The classification results in corresponding safety advice and conditions for the protection of the user.

Exclusion criteria for a classification in Category 2 are present if unlimitedly usable negative results in at least two laboratory animal species or exonerating arguments from studies of toxicokinetics or of effect mechanism, or convincing in vitro studies are available. Exoneration arguments can be:

- a) The toxic effect is detectable only in non-physiological exposure, e.g. after intraperitoneal or subcutaneous injection, but not with ways of administering relevant to practice.
- b) The toxic effect is based on mechanisms or biological preconditions that pertain to humans only to an extremely slight extent, if at all, and even with unfavourable exposure cannot lead to fetotoxic effects.
- c) Resorption, metabolizing and elimination of the substance in laboratory animals proceed qualitatively or quantitatively different than in humans.
- d) The increase in the incidence of maleformations related to the active ingredient cannot be delimited with certainty in comparison with historic controls, and refers predominantly to effects with high spontaneous rate that occur specific to strain and species in typical localization.

#### **18.7 Agricultural animals, mammals living in the open, birds**

Studies on toxicology, including reproduction toxicology of plant protection products in animals used in agriculture and mammals living in the open are not as a rule customary, and are required by the registration authorities only in exceptional cases. Data from toxicological studies in laboratory animals are used to assess the exposure to plant protection products.

In contrast, for determining maximum residue limits of plant protection products in foods of animal origin it is as a rule required that residue studies be conducted in ruminants, poultry and possibly swine. At least two dosages should be tested. If such studies are carried out over several days or weeks and clinical parameters are also examined, they can also be suitable for making statements regarding the tolerance of the active ingredient in the animal species affected.

For agricultural animals the level of the residues in feeds, such as in/on meadow grass, can be reduced by imposing waiting times until the cattle are driven to pasture. The mammals living in the open, however, protective measures such as fences against wild animals as a rule are not possible. For this reason, plant protection products the residues of which can, immediately after application or later, lead to irreparable injury or death in wild animals as a rule are not authorized.

Because of the differences in the physiological and anatomical situations in birds and mammals, toxicological data from studies with rodents can be used only to a limited extent for estimating the risk for birds. It is therefore internationally customary to test the range of acute toxicity for birds separately. For estimating an acute hazard, knowledge of lower threshold range of mortality is of greater significance than the exact determination of the LD<sub>50</sub> value. The Japanese quail has proven to be the laboratory animal of choice, since it is sufficiently sensitive, easy to procure and easy to handle.

As a rule it is sufficient to test the acute toxicity of the active ingredient and of the plant protection product on one bird species. For reasons of the comparability of the studies the same bird species should always be used, the Japanese quail being given preference. A scientifically plausible explanation for the necessity of a separate toxicological testing in aquatic birds (ducks) is not available. Acute toxicity studies and reproduction studies in ducks for the purpose of comparing with the corresponding studies with the Japanese quail or the bobwhite should therefore be omitted for reasons of animal protection.

For assessing the risk through granulated material, bait and treated seed uptake tests can become necessary (see Guideline 25-1 of the BBA in order to examine conditions of the formulation on the uptake behaviour of the birds. In addition to Japanese quail, ducks, pheasants or pigeons can also be used in such studies. From the behaviour of the birds with regard to the test sample as well as the occurrence of intoxication symptoms or deaths the possible risk that exists for birds in the open as a

result of exposure to the formulated grains can usually be recognized already in advance. It is considered probable and in part has been experimentally demonstrated that color, shape and or of the formulation can exert an influence on the uptake behaviour (see also Bundesgesundheitsbl. 27 no. 3, March 1984, pp. 67-76 and 30 no. 11, November 1987, pp. 381-392).

In order to recognize possible hazards of environmental chemicals and plant protection products for the health and reproduction of birds a six-week feeding test with Japanese quail is suitable. For plant protection products that in laboratory animals lead to impairment of reproduction or even to deformities, as a rule a testing for reproduction-toxic properties in birds should be carried out. Products used on large scale for the treatment of seed should likewise be examined in the afore-mentioned subchronic test processes for negative effects in birds.

For plant protection products which with authorized and proper use lead to acute intoxications of birds or pose such a threat, or which can represent a reproduction risk for birds, as a rule no agreement for authorization is granted.

### **18.8 Fish**

**Acute toxicity:** In the sense of a classification test the acute fish test makes possible the orientating assessment of the fish toxicity with short-term exposure. The acute toxicity to be tested for 96 hours for all plant protection product active ingredients in two fish species: rainbow trout and carp or another suitable cyprinidae.

The testing of the acute toxicity of the plant protection product in fish is particularly required when it can not be precluded that inert ingredients influence the toxicity. This means that especially plant protection products that contain emulsifiers, detergents, solvents or also several active ingredients must be tested for their toxicity toward fish (rainbow trout).

Determined from these investigations are the  $LC_{50}$ , the threshold concentration and the highest tested concentration at which after

the test (96 h) all fish are still alive. An active ingredient or a preparation is to be classified as "very ichthyotoxic" if the LC<sub>50</sub> (96 h) is less than 1 mg/l, and as "ichthyotoxic" if the LC<sub>50</sub> (96 h) is 1-10 mg/l.

In investigations on fish it is to be taken into consideration which active ingredient variant was tested, if an active ingredient has several variants. In addition, water-solubility, hydrolysis, decomposition, adsorption/desorption, photolysis and n-octanol/water distribution coefficient are also considered. Corresponding studies can also be required for ichthyotoxicologically relevant metabolites.

**Subacute toxicity:** The test serves to determine the highest concentration without observed effect (no-effect level) and should provide information on sublethal damage with the action of constant concentrations of the test substance.

For testing plant protection products in the subacute test a test duration of at least 21 days is currently required. In general, fish tests are currently conducted over 21 or 28 days with trout, because as a rule they react more sensitively than carp to plant protection products. To the extent that in exceptional cases a cyprinid in the acute test proves to be more sensitive than the trout to a plant protection product, the subacute test is then to be carried

out with the more sensitive fish species. As a matter of principle, for active ingredients in plant protection products that are to be used in the field longer-term studies on fish over at least 21 days are to be submitted. If it has been found in the acute toxicity test that a preparation is more toxic than the active ingredient, the longer-term studies must be carried out also with the preparation. In addition to the NOEC, the symptoms occurring during the entire period of the test and the other observations are studied and, where relevant, used for the assessment.

The "Fish Early Life Stage Test" is a more far-reaching test (e.g. over 60 days with trout) which after approval of an OECD test



guideline will be preferentially required. (In the past these studies were submitted only in isolated cases.)

**Chronic toxicity:** "Life-cycle tests" serve for recognition of fertility, growth and reproduction damage and provide essential evidence of possible population-damaging effects. They extend from the fertilization of the egg ( $F_0$  generation) to the young-fish stage of the  $F_1$  generation capable of feeding. Preferably species with short generation cycle (e.g. *Brachydanio rerio*) are suitable for chronic tests. For this reason, for example, the "life-cycle test" on *Brachydanio rerio* should encompass the exposure of the fertilized eggs for the  $F_0$  generation to the young-fish stage of the  $F_1$  generation capable of feeding. "Life-cycle tests" on native edible fish (carp, trout) are regarded as hardly practicable.

Chronic long-term tests serve to determine late damage and to determine the "no-effect level". The chronic toxicity studies can be necessary for plant protection product active ingredients that are difficultly decomposable in surface water, accumulate in fish or form toxic metabolites. Such a test is to be performed only if with authorized and proper use a long-term exposure of fish in water with relevant concentrations is to be expected (e.g. great expenditure amounts, great expenditure frequency, persistence of the substance), and as far this seems to be necessary according to the results of the tests on acute and subacute toxicity.

**Bioaccumulation:** The testing and assessment of the bioaccumulation in fish is also of significance for the use of fish as food. At present there can only be an individual-case decision taking into consideration the exposure of fish actually to be expected and the other toxicological properties of the active ingredient. If the  $\log P_{ow}$  is  $> 3$ , bioaccumulation tests with fish must be performed.