Evaluation Manual for the Authorisation of plant protection products and biocides

EU part

Biocides

Chapter 7 Efficacy

version 1.1; January 2013

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Board
for the Authorisation
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Chapter 7 Efficacy

Category: biocides
General

GENERAL INTRODUCTION

This chapter describes the assessment of the efficacy of an active substance for placement of this active substance on Annex I and the assessment of a biocide for product authorisation. For the evaluation of biocidal products only a general review is given. More specific information on the evaluation of the efficacy of specific product groups is given in separate chapters .
Furthermore, for both active substance and biocidal product, the assessment of data on unacceptable effects like resistance and unacceptable suffering caused by use against vertebrates is described.
This chapter only focuses on the EU framework.

1. EU FRAMEWORK

1.1. Introduction

Efficacy evaluation includes assessment of the following aspects:
- intended use (label claim)
- efficacy
- the occurrence of unacceptable effects on the target organisms, such as unacceptable resistance or cross resistance, or unnecessary suffering and pain for vertebrates [1].

The aspect efficacy has in EU framework been subdivided into two parts:
Efficacy of the active substance and efficacy of the product.

The data requirements as laid down in the Biocides Directive (98/8/EC) and the Technical Notes for Guidance (TNsG) on Product Evaluation and the TNsG on Annex I inclusion [2, 3] are listed below: the data requirements for the active substance and the product for evaluation of the label claim, efficacy, the occurrence of unacceptable effects – if any. This is the verbatim text of the Directive (grey frames). Numbering of the studies corresponds with the numbering of the TNsG on Product Evaluation and the Biocides Directive.

1.2. Data requirements

Article 8 Requirements for authorisation [1]
A dossier should as regards the aspect efficacy contain the following information:
(iii) intended uses:
3.1. product type (Annex V) and field of use,
3.2. category of users,
3.3. method of use

Intended use (claim)
The following information (outlined in Annex IIB) is likely (for most of the product types under scope) to form the basis of a label claim on the efficacy of a biocidal product [1]:
- product type
- spectrum of biological activity (including the (complexes of) target organisms and their development stage) and function (preventive, curative, maintenance, temporary)
- its mode of action (e.g. destroy, deter, render harmless, prevent the action of or otherwise exert a controlling effect on harmful organisms)
- area of use/site of application; geographical variability, limits and provisions concerning non-dominant targets and their tolerance for biocides
- duration of control/effect

- directions for use (including method(s) of application and application rate(s), time and duration of application); some products may be segmented in types of intended users: industrial, professional, amateur of the public at large
- other relevant information pertinent to the efficacy of the product (e.g. target dose rate, its variability and the application method), cf. Section 7.2.2.6

iv) Effectiveness data;
Annex IIA and IIB of 98/8/EC Guideline with Common core data state that the following data are required [1]:

Substance-specific data
V. Effectiveness against target organisms and intended uses
5.1. Function, e.g. fungicide, rodenticide, insecticide, bactericide
5.2. Organism(s) to be controlled and products, organisms or objects to be protected
5.3. Effects on target organisms, and likely concentration at which the active substance will be used
5.4. Mode of action (including time delay)
5.5. Field of use envisaged
5.6. User: industrial, professional, general public (non-professional)
5.7. Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies
5.8. Likely tonnage to be placed on the market per year

Product-specific data
V. Intended uses and efficacy
5.1. Product type and field of use envisaged
5.2. Method of application including description of system used
5.3. Application rate and if appropriate, the final concentration of the biocidal product and active substance in the system in which the preparation is to be used, e.g. cooling water, surface water, water used for heating purposes
5.4. Number and timing of applications, and where relevant, any particular information relating to geographical variations, climatic variations, or necessary waiting periods to protect man and animals
5.5. Function, e.g. fungicide, rodenticide, insecticide, bactericide
5.6. Pest organism(s) to be controlled and products, organisms or objects to be protected
5.7. Effects on target organisms
5.8. Mode of action (including time delay) in so far as not covered by Annex IIA, paragraph 5.4 EN 24.4.98 Official Journal of the European Communities L 123/31
5.9. User: industrial, professsional, general public (non-professional) Efficacy data
5.10. The proposed label claims for the product and efficacy data to support these claims, including any available standard protocols used, laboratory tests, or field trials, where appropriate
5.11. Any other known limitations on efficacy including resistance

The applicant should deal with all aspects mentioned above for annex I inclusion of the active subsatnce. For product authorisation only product-specific data are required.
Some general guidance is given here [2].

- The guidance on product evaluation in support of Annex VI of the Directive [1] (*see evaluation methodologies*) provides further amplification in this area. At the time of writing some detailed product type specific guidance is available for all product types and use patterns, further work still has to be done.
- The applicant must demonstrate that the biocidal product is effective and suitable for

its intended use when applied according to its instructions for use. This can be confirmed by provision of data that may include laboratory studies, pilot plant or field test data or other relevant study data, the test conditions of which are comparable with the purpose applied for and which are comparable with the environmental characteristics relevant for the intended use. Further product-type-specific guidance is given in the guidance document on product evaluation in support of Annex VI of the Directive.

- For field studies conducted outside the territory of the Member State in which the authorisation is being sought, a justification of the relevance of such data must be made. The extent of the information required will vary depending on the product type and proposed use pattern and upon the similarity of the conditions in the two countries. Justification may include, as relevant and appropriate, information on the harmful organism (e.g. comparison of genera/species and its relevance to the Member State in which authorisation is sought), meteorological parameters (e.g. mean temperatures and rainfall) and location details.
- The test method should measure a response and, as appropriate, an end-point relevant to the label claims. The method should employ a reference product for comparison, if possible, and an untreated control. The efficacy test reports should contain dose response data for dose rates lower than the recommended rate. However, this may not be always possible for field studies.
- Where earlier formulations of the product or other products containing the same active substance(s) are cited as supporting evidence, all relevant formulation details must be given and the relevance of this evidence to the current formulation must be fully justified.
- The tests (and data generated) should be based on sound scientific principles and practices. Compliance with quality standards such as GEP (Good Experimental Practice) and ISO 9000 is highly recommended. More detailed guidance on appropriate test methods is given in paragraph 52 of Annex VI in the Directive and in the associated guidance document.

A guidance document on use of efficacy methods is being developed by OECD (Overview of Efficacy testing methods for biocides. Draft 1999).

1.3. Assessment

The assessment of unacceptable effects and efficacy has been elaborated in the following documents:
The Biocides Directive 98/8/EC [1] Article 5 and 8, Annex VI 48-52 and 90-93
TNsG on Product Evaluation (Chapter 6, 7 and 8)
TNsG on practical procedures for the authorisation and registration of products (Chapter 6) , of which the part on resistance is recently revised (July 2009).
TNsG on Annex I inclusion
TNsG on data requirements (Chapter 2 B)

Further requirements concerning efficacy tests, available test methods and permissibility, and evaluation criteria for some product types are given in the separate chapters for these product types.

Appendix 1 and 2 of this chapter contain an elaboration from the TNsG on Product evaluation concerning “Animal Welfare” and aspects such as “resistance and cross resistance”.

1.4. Approval

Article 5, 1, b i) and ii) of the Directive of the European Parliament and the Council of 16 February 1998 concerning the placing of biocides on the market (98/8/EG) stipulates that Member States may only authorise a biocide if the product, when used consistent with the authorisation and taking into account:

- all conditions under which the biocide is normally used,
- the way in which material treated with the product can be used,
- the consequences of use and removal,

i) is sufficiently effective
ii) has no unacceptable effects on the target organisms, such as unacceptable resistance or cross-resistance or unnecessary suffering and pain for vertebrates,

1.4.1. Evaluation

The Common Principles (Annex VI of 98/8) present the starting points for evaluation as regards efficacy.
These concern the relevant parts of the introductory principles, the common principles, and the specific principles for the effects on the environment.
The specific principles for efficacy are in the text below printed in a grey frame. This text, including numbering, is the verbatim text of Annex VI of Directive 98/8/EC.

Unacceptable effects

48. Data shall be submitted to and evaluated by the Member State to assess whether the biocidal product does not cause unnecessary suffering in its effect on target vertebrates. This shall include an evaluation of the mechanism by which the effect is obtained and the observed effects on the behaviour and health of the target vertebrates; where the intended effect is to kill the target vertebrate the time necessary to obtain the death of the target vertebrate and the conditions under which death occurs shall be evaluated.
49. The Member State shall, where relevant, evaluate the possibility of the development of resistance to an active substance in the biocidal product by the target organism.
50. If there are indications that any other unacceptable effects may occur the Member State shall evaluate the possibility of such effects occurring. An example of such an unacceptable effect would be an adverse reaction to fastenings and fittings used in wood following the application of a wood preservative.

Efficacy

51. Data shall be submitted and evaluated to ascertain if the efficacy claims of the biocidal product can be substantiated. Data submitted by the applicant or held by the Member State must be able to demonstrate the efficacy of the biocidal product against the target organism when used normally in accordance with the conditions of authorisation.
52. Testing should be carried out according to Community guidelines if these are available and applicable. Where appropriate, other methods can be used as shown in the list below. If relevant acceptable field data exist, these can be used.

— ISO, CEN or other international standard method
— national standard method
— industry standard method (accepted by Member State)
— individual producer standard method (accepted by Member State)
— data from the actual development of the biocidal product (accepted by Member State).

1.4.2. Decision making

The Common Principles (Annex VI of 98/8) present the starting points for decision making as regards efficacy.
These concern the relevant parts of the introductory principles, the common principles, and the specific principles for the effects on the environment.
The specific principles for efficacy are in the text below printed in a grey frame. This text, including numbering, is the verbatim text of Annex VI of Directive 98/8/EC.

Unacceptable effects

90. If the development of resistance to the active substance in the biocidal product is likely the Member State shall take steps to minimise the consequences of this resistance. This may involve modification of the conditions of authorisation or even refusal of any authorisation.
91. An authorisation for a biocidal product intended to control vertebrates shall not be given unless: — death is synchronous with the extinction of consciousness, or, — death occurs immediately, or, — vital functions are reduced gradually without signs of obvious suffering. For repellent products, the intended effect shall be obtained without unnecessary suffering and pain for the target vertebrate.

Efficacy

92. Member States shall not authorise a biocidal product which does not possess acceptable efficacy when used in accordance with the conditions specified on the proposed label or with other conditions of authorisation.
93. The level, consistency and duration of protection, control or other intended effects must, as a minimum, be similar to those resulting from suitable reference products, where such products exist, or to other means of control. Where no reference products exist, the biocidal product must give a defined level of protection or control in the areas of proposed use. Conclusions as to the performance of the biocidal product must be valid for all areas of proposed use and for all areas in the Member State except where the proposed label prescribes that the biocidal product is intended for use in specific circumstances. Member States shall evaluate dose response data generated in trials (which must include an untreated control) involving dose rates lower than the recommended rate, in order to assess if the recommended dose is the minimum necessary to achieve the desired effect.

Efficacy

For decision making as regards efficacy, the TNsG on Product Evaluation [3] (Chapter 8) stipulates that for authorisation or registration of a biocide it should be established that the biocide:

- has no other unacceptable effects and is efficacious when used in accordance with its conditions of authorisation or registration;
- it is designed in such a way and comes with such information that it can be properly used, including application at an efficacious dose and at the minimum dose level required to exert the desired effect;

Evaluation of efficacy data on the active substance [3]
An active substance possesses a sufficient level of biocidal efficacy (for example fungicidal, insecticidal) at the recommended concentrations for use.

Recently the UK presented a paper in which a common approach is proposed for the efficacy evaluation of active substances for Annex I inclusion. This paper was accepted

in TMIV 2009. The following points are derived form this paper:

1. Efficacy data should be required on the active substance at the Annex I inclusion stage. These data should be able to demonstrate that the active substance has innate activity against a representative target species.

2. In line with the data requirements, efficacy data should also be required on the biocidal product at the Annex I inclusion stage. These should be able to demonstrate that the active substance has the ability to produce an effect on a representative target organism when it is included in a formulated product.

3. Where the innate activity of both the active substance and biocidal product against the target organisms has been demonstrated, a recommendation should be made for Annex I inclusion. In cases where activity has been demonstrated for the biocidal product, and where those activity levels would not be high enough for a Product Authorisation, the Applicant should be asked to defend why the levels of activity noted should be considered acceptable. Where the Applicant provides a satisfactory explanation, Annex I inclusion should still be recommended and the efficacy more fully addressed at the Product Authorisation stage.

4. It is not necessary to demonstrate efficacy against all of the target organisms at the Annex I inclusion stage, as additional target organisms may be added at Product Authorisation.

5. As only a minimal evaluation of efficacy takes place at the Annex I inclusion stage, a more comprehensive efficacy evaluation should be carried out at Product Authorisation.

6. The term “label claims” should be interpreted to include all claims made for the efficacy of the product, not just those on the product label itself.

During the meeting (TMIV09) several countries (including NL) commented on point 4, saying that at least for one use against one target organism efficacy levels should be high enough. However, since also dummy products are acceptable it was decided to accept the proposal above.

Evaluation of efficacy data on the product [3]
If the Rapporteur Member State is satisfied that:
- the assessment of biocidal activity of the candidate active substance demonstrates that the active substance has a sufficient level of efficacy against the target organism(s) avoiding unnecessary suffering of target organisms; and
- the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious, then the Rapporteur Member State can recommend inclusion of the active substance on to Annex I and/or Annex IA with respect to efficacy.

Resistance
For decision making as regards resistance the TNsG on Product Evaluation [3] (Chapter 6.2.5) states:

Having evaluated all the available data, the competent authority must determine whether resistance to the biocidal product is likely now or in the future, the significance of this in relation to performance, and possible management strategies to control the problem and

minimise any consequences. Based on this assessment the competent authority will decide which of the following will apply:

- authorisation/registration can be granted without specific conditions, because the data demonstrate a level of resistance which will have little effect on product performance, and the potential for any further development of resistance is low;
- the level of resistance or its development may affect product performance, but the biocidal product can be authorised/registered subject to specific conditions (e.g. a management strategy) or for a specific time period (followed by a review);
- a decision on authorisation/registration cannot be given until additional data/information are available to resolve a particular point or item of concern; or
- the biocidal product cannot be authorised/registered because product performance will be unacceptably affected by resistance, and/or the potential for the development of resistance is of concern and the proposed management strategy is considered inadequate to control it.

This decision must be a reasoned balance between the benefits of using a product and the loss of performance caused by any resistance problems (real or potential), taking into account the availability of other control methods and the implications of the loss of the product through refusal of authorisation (the wider the diversity of active substances that are available, the easier it will be to control future resistance problems).

- If resistance may occur, a resistance management strategy should be prepared (based on principles of integrated “pest control”) and applied to reduce or delay the chance of resistance.

2. APPENDICES

Appendix 1 Data from the TNsG on Product evaluation and the TNsG on Annex I inclusion concerning the prevention of unnecessary suffering of target animals

6.3 HUMANENESS

6.3.1 Introduction

"Humaneness" is a term which is difficult to define, but it infers the degree of pain, distress and discomfort to the target organism. Article 5(1)(b) of the Directive requires that products authorised for use against vertebrate target organisms will not cause them "unnecessary" suffering and pain. In other words, there must be a reasoned justification for the need for a product if that product is considered, from an evaluation of the submitted data, to cause suffering or pain. In particular, Annex VI of the Directive states that an authorisation for a biocidal product intended to control vertebrates will not be given unless:

- death is synchronous with the extinction of consciousness (although it is more important that exposure leads immediately to unconsciousness, and that consciousness is not regained), or
- death occurs immediately, or
- vital functions are reduced gradually without signs of obvious suffering.

The crucial aspects are the degree and length of suffering prior to unconsciousness and subsequent death. Therefore, the time necessary to obtain the death of the target vertebrate and the conditions under which death occurs shall be evaluated (Annex VI, para 48).

Annex VI also states that for an authorisation of a repellent product, the intended effect shall be obtained without unnecessary suffering and pain for the target vertebrate.

Suffering can be thought of as a specific state of "mind" which can be caused by pain or distress of sufficient intensity and/or duration. Pain can be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." In order to experience pain an animal has to be conscious, i.e. it must have an alert cerebral cortex. Distress can be defined as "a state where the animal has to put substantial efforts or resources into adaptive responses to challenges in the environment, and is failing to cope." It is usually caused by extremes in the animal's physical and social environment (e.g. heat or social aggression), and the degree of distress varies with the ability of the animal to cope with these. Some clear criteria for defining when changes indicate severe distress have been published (e.g. Anon, 1994).

Pain and distress are states of adverse subjective experience and cannot be measured directly. However, an assessment can be made based on an animal's overall pattern of physiological and behavioural responses, a knowledge of the mode of action of the active substance, and post-mortem reports.

6.3.2 Types and availability of data

6.3.2.1 General requirements

No internationally agreed test guidelines exist. However, it is recommended that the competent authority makes decisions on humaneness based on existing data wherever possible, including:

- any information relating to the experiences of humans clinically treated with, or otherwise exposed to (e.g. at the workplace), the candidate product or other products containing either the same active substance or ones with similar chemical structures and/or suspected modes of action (it is assumed that conditions which are known to cause pain

in humans do so in other vertebrates unless convincing evidence is available to the contrary); and

- any information on the humaneness, toxicity and efficacy of the candidate product or its active substance, or of active substances with similar chemical structures and/or suspected modes of action, in the target species or any related species, which may be of use in assessing the humaneness of the product. In this respect, emphasis should be placed on using **the existing data set** for the active substance and the product, and literature searches. Humaneness information should, where possible, be obtained from the acute mammalian toxicity tests, acute ecotoxicity tests and/or efficacy studies on the product using laboratory strains of the target species.

The competent authority must assess the relevance of this information for the candidate product, particularly where the data do not directly concern the candidate product or its active substance, or the proposed target species. If a decision can be made on the likely suffering of wild animals based on data obtained using laboratory strains, the competent authority may decide that no further testing is required. Similarly, if the need for the product is fully justified, further testing would not be appropriate (see section 6.3.5).

Confirmatory humaneness testing of the product on the target species should therefore **not normally be required**. If, following a review of the data, the competent authority decides that further confirmatory testing is required, it should provide a full justification. Such testing should only involve small scale experiments using wild caught animals, or wild animals bred in captivity, housed in environments that approximate in important respects (e.g. temperature, lighting, food, social grouping, etc.) to the natural habitat. Procedures should initially involve low doses, in order to minimise the likely severity of suffering, and doses should not go beyond that on the proposed label for commercial use. The competent authority must inform the applicant of its decision, and if further testing is necessary, agree on an acceptable programme with them. The test programme should comply with European and national legislation on animal welfare (i.e. Directive 86/609/EEC).

6.3.2.2 Details to be included in a test report

No formal guidelines for studies to investigate humaneness exist. It is recommended that the competent authority should expect the test report to contain the following details, where relevant (this list is not exhaustive):

- details of species, genetic strain, age, sex, weight, reproductive history and origin (whether wild-caught or hand-reared, etc.) for each experimental animal;
- a description of the environmental conditions (and uncontrolled external influences) before and during trials, including diet and stocking details;
- dose levels and method of delivery (with vehicle used, if applicable, and concentration in the units expressed on the proposed product label);
- the time to death (and conditions under which death occurs, including clinical observations) after dosing for each animal, where the intended effect is to kill the target vertebrate;
- the time to insensibility after dosing for each animal, where the intended effect is to make the target vertebrate unconscious, and the time to regain sensibility prior to death or full recovery as appropriate;
- **a range of appropriate observations concerning the degree and duration of suffering while the animal is conscious prior to either death or full recovery** (e.g. for repellents and sub-lethal exposure). The circumstances, appearance, performance and behaviour patterns of test animals should be recorded as objectively as possible at regular intervals before, during and after dosing, using appropriate scales with

accompanying descriptive information where relevant;

- reasons and criteria used for killing of test organisms in order to avoid unacceptable suffering (e.g. when an animal develops grossly abnormal behaviour such as self-mutilation); and
- the training and experience of personnel conducting the experiments, with details of precautions taken against observer influence.

6.3.3 Evaluation

The applicant's data submission should include all information necessary to allow an evaluation of the humaneness of the biocidal product to the target organism (including the mechanism by which the effect is obtained) at the recommended dose/application rate, when used in accordance with the label instructions. The competent authority will evaluate the data and consider the duration and severity of any symptoms caused by the proposed normal use of the product, and whether they demonstrate that (where relevant):

- death is synchronous with the extinction of consciousness1, or
- death occurs immediately, or
- vital functions are reduced gradually without signs of obvious suffering.

Suitable criteria must be used to judge the severity of symptoms (e.g. Anon, 1994)). It should be assumed that increased severity or duration of symptoms increase the degree of distress which in turn decrease the degree of humaneness. In addition, it is essential that physiological data are assessed in the light of behavioural information because some phenomena frequently associated with pain (such as dilation of the pupils) can occur in animals after the cerebral cortex has been destroyed.

The competent authority should perform the evaluation with regard to:

- test objective;
- study content and methodology (including use of controls and reference products, test procedures, results and analysis, etc.);
- acceptability of the method;
- robustness;
- quality assurance;
- completeness; and
- adequacy (i.e. its reliability and relevance to the proposed use of the candidate product).

Expert judgment is needed for proper interpretation of humaneness data in view of the complexity of the issues. Examples of complicating factors include:

- products with analgesic properties (a target organism rendered insensitive to pain may still suffer through high levels of stress or discomfort);
- palatability (target organisms which find a product unpalatable may only receive a sub-lethal dose in the field situation, and consequently they experience different degrees of suffering than if they had taken a lethal dose);
- misleading symptoms (e.g. a decrease in blood pressure through blood loss may result in symptoms which appear to indicate sedation whereas in fact the animal may still be conscious and experiencing pain); and
- behaviour (this may be affected by factors that are not product-related, such as human

1 It is in fact more important that exposure leads immediately to unconsciousness, and that consciousness is not regained.

disturbance or social stress, and there are differences between species, strains and individuals).

In addition, the humaneness of the entire control procedure may need to be considered on occasion, e.g. for methods that involve capture of the animal before administration of the biocidal product. In these cases, the method and competence of capture and the transfer of the animal to the application container will have at least as great an influence on the humaneness of the technique as the effects of the biocidal product itself.

Conclusions as to the performance of the product must be valid for all areas of the Member State in which it is to be authorised and must hold for all conditions under which its use is proposed. Decisions may also need to be made regarding read-across of humaneness data for similar species, especially where the intention is to extend the label claim.

6.3.4 Examples

Humaneness needs to be considered for all products used against vertebrates:

- *Product type 14:* Rodenticides
- *Product type 15:* Avicides
- *Product type 17:* Piscicides
- *Product type 19:* Repellents and attractants
- *Product type 23:* Biocidal products used to control other vertebrates (e.g. moles and rabbits)

In addition, humaneness must be considered for vertebrates that are treated with biocidal products to control non-vertebrate target organisms:

- *Product type 3:* Veterinary hygiene biocidal products
- *Product type 19:* Repellents and attractants

6.3.5 Decision making

The competent authority must determine whether any suffering caused by the biocidal product is unavoidable (including any considerations for replacing the product or refusing an authorisation) and therefore "necessary" (see section 6.3.1).

For products that are intended to harm the target animal, the consideration of the humaneness data must take account of

- the type of product and its mode of action;
- the availability of alternative treatments;
- the scale of usage of the material;
- the significance of the pest;
- the presence of resistance; and
- any special factors.

For products not intended to harm the target animal (e.g. repellents), a case must be made to justify the acceptability of the humaneness data for each product.

Based on this assessment the competent authority will decide which of the following will apply:

- authorisation/registration can be granted without specific conditions, because the data demonstrate a level of vertebrate suffering which is justified by the intended use;
- authorisation/registration can be granted with conditions of use, because the data demonstrate a level of vertebrate suffering which is justified provided the conditions are met (e.g. specific methods of bait delivery to ensure that a lethal dose is administered);

- a decision on authorisation/registration cannot be given until additional data/information are available to resolve a particular point or item of concern; or
- the biocidal product cannot be authorised/registered because the level of vertebrate suffering is unjustified and cannot be reduced to an acceptable level by restrictions on use.

This decision must be a reasoned balance between the benefits of using a product and the level of humaneness, taking into account the availability of other control methods and more humane alternatives, and the implications of the loss of the product through refusal of authorisation/registration.

6.4 OTHER EFFECTS

6.4.1 Introduction

Annex VI of the Directive requires the competent authority to evaluate the possibility of any other unacceptable effects occurring if there are indications that they may do so.
This section is therefore concerned with those unacceptable effects that may affect performance but do not involve target organisms. It should be noted that many possible effects that could be included in this category (such as tainting of foodstuffs and discolouration of surfaces), whilst undesirable, are not related to product safety and so should not be considered as part of the authorisation process.

The competent authority should therefore evaluate other effects only if they are directly linked to human, animal or environmental safety, and there are indications that they may occur. It is the duty of the applicant to provide all relevant information on hazards that are not obvious from use of the product. **For most products it is expected that 'other' effects will not need to be considered.**

6.4.2 Types and availability of data

Due to the types of effects which may occur the requirements supporting data generation must be flexible. Effects data may arise from specific tests, or may be inferred indirectly from non-specific tests, but it is expected that data will often only arise from experience in use. The effects considered must be relevant to the intended use of the product when applied as directed by the label.

Evidence of effects may come from:

- laboratory studies (including simulated use tests), e.g. from product development trials or tests required for either Annex I/IA inclusion of the active substance or product authorisation;
- field studies (in which data are generated in the actual service conditions and in the manner described on the product label); or
- other sources, e.g. information in industry codes of practice or safety data sheets.

When a particular effect is suspected from circumstantial evidence, a confirmatory test may be desirable. Relevant data may be available for individual product components (including the active substance), and specific information may also be available for either the candidate product or products containing similar ingredients.

6.4.3 Evaluation

The applicant's data submission should be sufficient to allow the competent authority to perform a reasonable evaluation of the likelihood of the occurrence of relevant effects at the recommended dose/application rate, when the product is used in accordance with the label instructions. In general, the competent authority should expect the applicant to have shown

that they have considered all relevant effects which can reasonably be expected from the nature of the product. In addition, particularly when the effect is inferred indirectly from other data, the competent authority must assess whether it is likely to occur in real-life situations.

It is expected that expert judgment will play a large part in the proper interpretation of data. For example, some biocidal products are highly surface-specific and will not move into another material in close proximity. Where there is doubt, the competent authority may need either corroborating data, or evidence to show that other possible causes of the effect have been excluded. Conclusions as to the performance of the product must be valid for all areas of the Member State in which it is to be authorised and must hold for all conditions under which its use is proposed.

6.4.4 Example

An example of the type of effect that needs to be considered is the increased risk of corrosion of certain types of metal fixings in timber on exposure to some wood preservatives when applied wet (e.g. copper/chromium/arsenic wood preservatives can affect both ferrous metal and uncoated aluminium fittings - see BS 4072: Part 2: 1987 and BS 5268: Part 5: 1989 for further information).

6.4.5 Decision making

The acceptability of the effect depends to a large extent on the likelihood of its occurrence and its significance. Based on the assessment the competent authority will decide which of the following will apply:

- authorisation can be granted without specific conditions, because the data demonstrate that all identified undesirable effects will have little impact on product safety in practice due to their low significance and/or their low probability of occurrence;
- the undesirable effects may affect product safety, but the biocidal product can be authorised subject to specific conditions;
- a decision on authorisation cannot be given until additional data/information are available to resolve a particular point or item of concern; or
- the biocidal product cannot be authorised because product performance will be unacceptably affected even with restrictions on use.

This decision must be a reasoned balance between the benefits of using a product and the lowering of safety (real or potential) caused by the effect(s), taking into account the availability of other control methods (see Chapter 8).

In practice it is expected that no authorisation would be refused on the basis of such undesirable effects alone. Instead, authorisation is more likely to be subject to specific conditions (e.g. label warnings) which may be tied in with controls for other effects. For the wood preservative example given above:

- the label may need to include advice to avoid fitting fixings for a certain time period after treatment until the fixation of these preservatives is complete, or until the moisture content of the timber has fallen below a certain level (depending on the intended service life of the component and likelihood of dampness).

Appendix 2 Data from the TNsG on Product evaluation and the TNsG on Annex I inclusion concerning the occurrence of resistance and cross resistance (version July 2009)

6.1 GENERAL INTRODUCTION

6.1.1 Background

The evaluation of unacceptable risks to humans, animals and the environment (including to non-target organisms (e.g. beneficial insects) and the atmosphere (e.g. ozone depletion)) are dealt with in Chapters 3-5. This chapter provides guidance for the assessment of other effects which contribute to the overall performance of the product but which are not directly linked to its intrinsic properties or efficacy.

In accordance with Article 5 (1) (b) of the Directive, the competent authority must assess the potential unacceptable effects of the product on target organisms, such as unacceptable resistance, and any unacceptable suffering caused by use against vertebrates. Annex VI also requires competent authorities to evaluate the possibility of any other unacceptable effects occurring if there are indications that they may do so.

6.1.2 Objective of the guidance

This chapter, used together with expert scientific judgment, gives guidance for competent authorities on the evaluation of unacceptable effects data so they can decide how these will influence the authorisation.

The range of potential unacceptable effects is very broad and there are no internationally agreed guidelines for their assessment. In addition, relevant information can be complex, and may be obtained from a variety of sources. Consequently the guidance is of a general nature and information for each product must be assessed on a case by case basis. Detailed information about specific properties and effects is available in a variety of reference texts (e.g. Buckle & Smith, 1994).

Resistance, humaneness and 'other' effects are dealt with in three separate sections, and particular attention is paid to the types of data which might be available and the decision making process. **In all cases it is the responsibility of the applicant to provide all relevant information for the competent authority, in a structured and readily accessible format.** The guidance is valid for all countries in the European Union. However, situations within certain territories may vary due to different working practices, environmental conditions, and the relevance and breeding biology of the target species.

6.2 RESISTANCE

6.2.1 Introduction and Definitions

Annex IIA of the Directive requires information on the occurrence and possible development of resistance, and appropriate resistance management strategies, for chemical active substances. Annex IIB of the Directive requires information on any known limitations on efficacy of the biocidal product including resistance.

The evaluation of resistance must be done on a case-by-case basis taking into account the possible development of resistance (see chapter 6.2.3.3). A number of factors need to be considered:

The term resistance refers to a genetically inherited characteristic, which cannot be acquired during the lifetime of the organism. **Resistance** can be defined as a heritable

decrease in susceptibility or a lack of susceptibility of an organism to a particular treatment with an agent under a particular set of conditions. The term ‘resistance’ is often used loosely, and incorrectly, to explain treatment failure which may be attributed to inadequate treatment, behavioural changes of the target pest, target pest tolerance or other contributory factors.

One has to distinguish between **acquired resistance**, i.e. when the decreased susceptibility or insusceptibility is the result of genetic changes due to mutation or the acquisition of appropriate genetic material (e.g. plasmid coded resistance genes in bacteria), and **intrinsic resistance**, an already existing, inherent property of a certain species resulting in low or insusceptibility. Another distinction can be made between **stable** and **transient resistance,** considering reversibility of the resistance. From this point of view, transient resistance results from a temporary adaptation induced by the changes of the environment (stress).

An important phenomenon is the occurrence of **cross resistance**: wherever a species develops resistance to a particular active substance, it may also be resistant to other active substances to which they have not previously been exposed, due to (i) chemical similarity of the compound having the same mode of action, (ii) in case of overlapping targets or (iii) low specificity of the resistance mechanism. Laboratory studies have shown the possibility of cross-resistance between biocides and antibiotics, and between biocides themselves.

Different from cross resistance is **co-resistance**. Co-resistance refers to the presence of several resistance mechanisms in the same organism (also designated as multi-resistance). The corresponding genes are adjacent (physically linked) and expressed in a coordinated fashion.

The **level of resistance** of a particular genetic strain can be quantified in laboratory studies by the resistance factor (or ratio), which is the number of times the amount of biocide given to a resistant strain has to be increased above the normal dose to achieve the same effect as that dose in the normal strain.

For antibacterial biocides, the nature and the level of resistance of a particular microbial strain can be assessed in laboratory studies by using the Minimum Inhibitory concentration (MIC) (or Minimum Bactericidal Concentration / Minimal Fungicidal Concentration), the changes of the bactericidal kinetics, and the molecular biology techniques to detect the genes responsible of the resistance.

The level of resistance, its geographical spread and frequency of occurrence can all change with time for any one biocide (indeed there can be a wide variation in resistance levels across a single country). It should be noted that some biocides will continue to have a commercial usefulness even at reduced levels of efficacy towards a particular target species.

Intrinsic resistance should be detected during efficacy testing of biocidal compounds and could therefore be regarded as not being a subject for an assessment for the potential for resistance. Intrinsic resistance may, however, remain undetected, if test measurements are not sufficiently related to the treatment conditions that prevail under practical conditions, or when certain factors, that render insusceptibility, are simply unknown.

Unlike intrinsic resistance, that appears unexpectedly solely when the underlying conditions or factors leading to a decreased susceptibility were formerly unknown, acquired resistance in fact turns up newly in a population of a pest organism. Since acquired resistance develops after a certain period, it cannot be detected by efficacy testing of a new active substance or biocidal product in advance.

Resistance Mechanisms

Three main types of resistance mechanisms are presently known:

1. **Detoxification** of active compounds by the production of degrading or modifying enzymes.
2. **Target-site alteration**, i.e. modification of the target molecule that is "attacked" by the active compound.
3. **Reduced uptake** into the body or **decreased penetration** mainly of antimicrobial compounds by impermeability and efflux pumps - passive, which involves alterations of outer membrane structure, decreasing the rate of entry of active compounds and over expression of efflux pumps that exports the active compound outside the cell. In this way organisms can become resistant to many different compound classes (cross resistance).

In higher organisms like insects or rodents, changes in susceptibility are based almost exclusively on acquired resistance through genetic changes.

Treatment failure as a result of **behavioural changes** of the target pest can be displayed in a number of ways, such as bait preference and neophobia. Behavioural changes do not involve actual systemic resistance to a biocide's action, and it can be reversible.

An example of bait preference is the altering of feeding habits from protein to carbohydrate baits. Obviously if bait preference changes or is different depending on the change in the life cycle of the pest, then the biocidal product will have varying degrees of efficacy.

Neophobia or "new object reaction" is exhibited by some rodent species, and refers to individuals who avoid a new object (such as a bait) placed in the environment until they become used to it. As a result the individual may only take a small, sub-lethal amounts of bait, and may consequently avoid the bait if it learns to associate it with an unpleasant response.

Some of these behavioural aspects can be anticipated and tested through experimental design when biocidal products are being developed but others can only be overcome by the expert use of the biocide by trained professional operators.

Tolerance can be defined as the ability of an organism to withstand the effect of a normally lethal dose of a biocide by ingestion of increasingly large sub-lethal doses over a short period of time.

Tolerance is different from resistance because if the normal lethal dose is administered in single dose the individual will die (resistant individuals will not).

For bacteria, the term tolerance is frequently used for specific mechanisms leading to a maintaining of the inhibitory of growth activity but a loss of bactericidal efficiency i.e. for ß-lactams against some *Staphylococcus aureus* strains.

It can be seen from the above points that the potential for actual resistance must be identified to establish that a resistant management strategy is required.

Where relevant the Competent Authority should evaluate the extent and nature of existing resistance to an active substance by the target organism, and anticipate its development, so that a balanced Annex I inclusion decision can be made.

6.2.2 Types and availability of data

Whilst data should be relevant to the target species, requirements must be flexible because of the variable nature of resistance. Evidence of resistance may come from:

- laboratory studies specifically addressing resistance (including determination of mutation frequency, simulated use and dose-response tests), e.g. efficacy studies on strains which are known to be resistant to the active substance. For vertebrates there may be specific, non-lethal methods of resistance assessment, such as blood clotting tests for rodenticide anticoagulants; or

- field studies (in which data are generated using the product in the actual service conditions and in the manner described on the product label). Field observations may also be provided as additional evidence (however, see section 6.2.3.1).

- Resistance data will usually be available for existing active substances following review for Annex I inclusion, but there are unlikely to be any data for new active substances. However the Competent Authority may be able to make a decision based on relevant information on products containing an active substance from the same chemical class with a similar mode of action against similar target organisms.

If valid data are available in connection with resistances to existing active substances, these should be added or references made to the relevant publications. These data will usually be available for existing active substances following review for Annex I/IA inclusion, but it is unlikely that there will be any data for new active substances. However, the competent authority may be able to make a decision based on relevant information on products containing an active substance from the same chemical class with a similar mode of action. Similarly, data are not necessarily required for every product because an extrapolation may be possible from data on similar products containing the same active substance.

6.2.3 Evaluation

6.2.3.1 General principles

The applicant's data submission should include, where relevant, all information necessary to allow a reasonable evaluation of target organism resistance to the biocidal product at the recommended dose/application rate, when used in accordance with the label instructions. Data on the active substance itself will have been considered at the Annex I/IA inclusion, and must not be re-interpreted. Where product data are provided, the competent authority should perform the evaluation with regard to:

- test objective;

- spectrum in reference to the claim;

- study content and methodology (including use of controls and reference products, test procedures, results and analysis, etc.);

- acceptability of the method;

- robustness;

- quality assurance;

- completeness; and

- adequacy (i.e. its reliability and relevance to the proposed use of the candidate product)

- field data from any source should be taken into account.

Expert judgement is needed for proper interpretation of resistance data. For example, data generated on laboratory strains may not be reliably extrapolated to wild individuals in the field situation. In addition, field observations should be viewed with caution. For

example, persistent infestations are often caused by re-invasion from untreated surroundings or poor application techniques rather than resistance. Apparent resistance may also be caused by behavioural factors, such as neophobia (as is often the case for rats). For this reason, the competent authority will need evidence to show that other possible causes of treatment failure have been excluded. Corroborating data would usually also be needed from laboratory tests on captured specimens.

Conclusions about the performance of the product should usually be valid for all areas of the Member State in which it is to be authorised, and all conditions under which its use is proposed. However, where there are pockets of resistance within a Member State's territory, the competent authority should decide whether continued use of the product can be allowed elsewhere within the territory (e.g. it may be possible to contain the resistant pockets by a suitable management strategy (see 6.2.3.4)). Decisions may also need to be made regarding read-across of resistance data for similar species, also from other genus or families in the case of microorganisms, especially where the intention is to extend the label claim.

6.2.3.2 Cross-resistance

The problem of cross-resistance also needs to be addressed for products. This will be necessary when the active substance has a similar mode of action or mechanism of resistance (i.e. porins modification in Gram negative bacteria) or belongs to a particular chemical class, which is known to cause resistance problems in particular situations (e.g. pyrethroids used to control fly problems in intensive animal units). Information on known resistance problems with related active substances should be provided in meeting the Annex IIA data requirements for the active substance. In such cases, the competent authority should ensure that adequate data on the activity of the product against these resistant strains have been provided.

6.2.3.3 Development of resistance

As well as assessing the immediate likelihood of resistance for the product, the competent authority must, where relevant, evaluate the possibility of the development of resistance to the active substance by the target organism. This will normally be considered at the Annex I/IA inclusion, but it may be appropriate to consider this for particular products as well. However, it is likely that resistance development will only become evident as the product is used. The ability of laboratory tests to predict such development can be relatively low, because they often show only the symptoms of resistance rather than the underlying cause or because resistance has not been established in the genetic pool within the relatively short duration of the test. Factors that may promote the development of resistance are related to the mode of action of the active substance, the lifestyle of the target organism and the proposed use pattern of the biocidal product. Examples of such factors include:

- active substances that act by a "one site" (as opposed to a "multi-site") mechanism;
- active substances able to induce a high frequency of mutation;
- target organisms with rapid breeding cycles (i.e. many generations per year);
- pest infestations that are confined in some way (where resistant individuals are unable to disperse and so remain localised);
- use of the biocide over large areas and/or for long periods with frequent application rates (creating a continual evolutionary selection pressure on the target population);

- use of the biocide over biofilm;
- use of a number of biocidal products against the same pest which contain either the same active substance or active substances with similar modes of action;
- use of active substances that expose “multi-generations” of the target organism as opposed to single generations to one application is more liable to cause resistance.

As regards **acquired resistance**, the two basic factors that affect the probability of the emergence of new resistance traits are related to the mode of action of the active substance and to the biology of the target organism:

(i) **The specificity of the biocide mechanism** (the likelihood of resistance development generally increases with the specificity of the biocide mode of action), and
(ii) **The reproduction rate of the target organisms** (the likelihood of resistance development increases with the turnover rate of generations and the population size).
In addition, a number of important conditions and factors that have to be considered are related to the use pattern of the biocidal product:
(iii) **Site of application** - confined, closed areas (e.g. laboratory equipment) where a thorough elimination of pests are intended (no or very low survival rate) are less prone to resistance development than open, unconfined areas, where the number of individuals can only be reduced to an acceptable level.
(iv) **Controllability of exposure**, controllable use ensures the appropriate and regular way of application. Uncontrolled use of the biocide in an inappropriate way – too low doses and/or too short time – may not only lead to the survival of target organisms with an inducible intrinsic (cross-) resistance, but may as well lead to the enrichment of genotypes with an elevated tolerance towards the given agent.
(v) **Use of the biocide** – is it intended to use the product over large areas and/or for long periods with frequent application rates? Such treatments create a continuous evolutionary selection pressure on the target population. It is widely agreed that the most efficient way to delay the development of drug resistance remains the reduction of selection pressure, i.e. decreasing the number of treatments. Are there biocide residues on surfaces? Is there some interference between the biocide and the soil surfaces (decreasing the efficacy by lessening the effective concentration)?

6.2.3.4 Resistance management strategies

Where resistance is considered likely to be a problem for use of a particular active substance at the Annex I/IA inclusion, an overall management strategy should be implemented in order to help delay or reduce the likelihood of resistance development, and minimise any consequences. The competent authority must evaluate the proposed use of the product in the light of any strategy recommended at the time of the Annex I/IA inclusion, and where necessary ensure that the applicant submits a supplementary management strategy for particular products (such a strategy may be based on the principles of integrated pest control, but should be distinguished from actions which are tailored to control site-specific resistant infestations).

The competent authority must assess these proposals to determine their acceptability, and whether they are appropriate to the use of the product, on a case by case basis. For example:

- a strategy which aims to limit the number of resistant individuals rather than eradicate them may be suitable for housefly control in intensive animal units but would not be acceptable for the control of cockroaches in food-handling premises.

What is a resistance management strategy?

The immediate aim of resistance management is to prevent or retard the development of resistance to a given biocidal active substance while permitting its continued use, as far as possible without being counterproductive. The ultimate aim is to reduce or eliminate the adverse consequences of resistance. The central concept is that this can be done more effectively and cost-efficiently by integrated, cohesive and systematic action than by the normal, default option in which all the parties involved improvise their own ways of addressing the problem. In this sense the approach has much in common with IPM (integrated pest management), and uses the same wide range of techniques.
Where relevant, contact should be sought with the International Resistance Action Committees (RACs)[2]
Because the emergence of resistant individuals is a natural phenomenon and therefore unavoidable, the only means to manage resistance development is to prevent or to delay the dissemination of resistant target organisms (or the resistance genes) by appropriate measures, that match the above mentioned fixed conditions and factors, and that are comprised of a specific mode of pest treatment and of surveillance of resistance spread.

The appropriate measures and procedures that would be adequate for biocides do not in general differ from those that have been suggested for pesticide use (EU Directive 91/414/EEC) and that have been outlined and discussed in detail in a number of contributions published by the Resistance Action Committees (RACs). The main objective and purpose of these measures can be summarized as:
(i) minimize the selection pressure as far as possible, but
(ii) take care not to apply sub lethal doses allowing better adapted individuals to survive.
Without question, the deployment of a suitable range of alternative active substances is necessary for the management of resistance and to prolong the useful lifespan of those active substances to which resistance has become a problem. The following practices are among a number of the more feasible options available to retard the onset of resistance, where resistance is identified as a significant problem:

- the incorporation of appropriate label warnings or provision of other labelling advice, for example not using the biocidal active substance in isolation. Consideration of application with one or more biocides of a different type (biocidal diversity), or as one component in a rotation of different treatments.

- Restriction of the number of treatments applied, and application only when strictly necessary. Special requirements could be defined for disinfectants and general biocidal products (main group 1), as related resistance is affected by several factors such as concentration, temperature, type and time of application.

- Use of non-chemical control techniques, where available.

- A switch to another biocidal active substance to which resistance rarely or never develops (or alternance).

- Ensuring complete eradication with a specific biocide and resuming the current treatment (or association).

- Maintaining uncontrolled, susceptible populations in refugia (in isolated areas) from which emigration can occur.

[2] The RACs give advice on the use of pesticides (www.rrac.info; www.frac.info; www.irac-online.org) It will often be easy to broaden their field of work to biocides, such as in the cases of fungicides and insecticides which are used both in pesticidal and biocidal applications.

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- specific conditions of authorisation, e.g. restrictions on the use of the active substance(s) in a particular situation or geographical area.

Note: These are general measurements on how to manage resistance. Supplementary strategies may be required later for individual products (see TNsG for product evaluation for further information).

Resistance Monitoring

When resistance has been detected and a resistance management strategy instituted, monitoring is necessary to determine its effectiveness. Some form of surveillance, such as questionnaire surveys, investigation of reports of inefficiency, or some other form of feedback reports, may also help towards early detection of new cases of resistance.

6.2.4 Examples

Resistance should be considered for all product types where there is a possibility of its development (this will usually be identified at the Annex I/IA inclusion for the active substance). The following list gives some examples of product types with well-known resistance problems, but it is not exhaustive.

Product type 14: Rodenticides

e.g. resistance of rats to first and second generation anti-coagulant rodenticides.

Product type 18: Insecticides, acaricides and products to control other arthropods

e.g. resistance of houseflies to synthetic pyrethroid insecticides in intensive animal units.

In addition, biocidal products for control of micro-organisms may be prone to resistance problems. Relevant product types include disinfectants (Product types 1-5), preservatives for liquid cooling and processing systems (Product type 11), slimicides (Product type 12) and metal-working fluids (Product type 13).

6.2.5 Decision making

Having evaluated all the available data, the competent authority must determine whether resistance to the biocidal product is likely now or in the future, the significance of this in relation to performance, and possible management strategies to control the problem and minimise any consequences. Based on this assessment the competent authority will decide which of the following will apply:

- authorisation/registration can be granted without specific conditions, because the data demonstrate a level of resistance which will have little effect on product performance, and the potential for any further development of resistance is low;
- the level of resistance or its development may affect product performance, but the biocidal product can be authorised/registered subject to specific conditions (e.g. a management strategy) or for a specific time period (followed by a review);
- a decision on authorisation/registration cannot be given until additional data/information are available to resolve a particular point or item of concern; or
- the biocidal product cannot be authorised/registered because product performance will be unacceptably affected by resistance, and/or the potential for the development of resistance is of concern and the proposed management strategy is considered inadequate to control it.

This decision must be a reasoned balance between the benefits of using a product and the loss of performance caused by any resistance problems (real or potential), taking into account the availability of other control methods and the implications of the loss of the product through refusal of authorisation (the wider the diversity of active substances that are available, the easier it will be to control future resistance problems).

3. REFERENCES

1. Biocides Directive (98/8/EC).
2. TNsG on Annex I inclusion. 2002. Technical Notes for Guidance in Support of Directive 98/8/EC of the European Parliament and the Council Concerning the Placing of Biocidal Products on the Market. Principles and Practical Procedures for the inclusion of active substances in Annexes I, IA and IB. April 2002
3. TNsG on Product Evaluation, FINAL DRAFT, Version 10.0, July 2002. Common principles and practical procedures for the authorisation and registration of products.
4. Data requirements for biocidal product types FINAL DRAFT. Version 4.3.1 April 2000, Chapter 2. common core data set for active substances and biocidal products