

THE ROLE OF EFFICACY IN THE EVALUATION OF ACTIVE SUBSTANCES FOR ANNEX I INCLUSION

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1 INTRODUCTION

The Review Programme for biocidal active substances is now well under way; several new active substances have been evaluated for Annex I inclusion and the first Product Authorisations are imminent.

However, the work conducted by Member States so far has highlighted a number of inconsistencies with the efficacy evaluation of active substances and biocidal products.

At present, different Member States are requesting different information for Annex I entry, which may be due to the inconsistencies and contradictions that exist in the current Technical Notes for Guidance (TNsG).

In addition, while efficacy is included in the evaluation for Annex I inclusion, most of the detailed evaluation work is being deferred to the Product Authorisation stage.

A common approach to efficacy evaluation within the BPD process, both at Annex I entry and at Product Authorisation, was introduced at the Technical Meetings III 2009 based on a proposal of the UK and approved at the Technical Meeting IV 2009.

2 PROBLEMS WITH THE CURRENT SYSTEM

2.1 EFFICACY DATA REQUIREMENTS

2.1.1 ACTIVE SUBSTANCES

2.1.1.1 TNSG ON DATA REQUIREMENTS

At present, the existing guidance provides contradictory information on the need for efficacy data to support the active substance.

The Technical Notes for Guidance on Data Requirements deals with the efficacy data requirements for active substances in:

- Chapter 2 (*Common Core Data Set for Active Substances and Biocidal Products*)
- Part A (*Common Core Data Set for Active (Chemical) Substances*)
- Section 5 (*Effectiveness against Target Organisms and Intended Uses*)

This section does not include a requirement for the submission of efficacy data on the active substance. The introduction to this section states:

Information on the effectiveness and intended uses of the active substance must be sufficient to permit an evaluation of the product, including the nature and benefits that accrue following use of the substance in comparison to suitable reference substances or damage thresholds, and to define its conditions of use. Actual efficacy studies are required in Section B5, data set for the biocidal product.

The first sentence states that “information” on the effectiveness of the active substance must be available, but the final sentence implies that this information should not be in the form of “actual efficacy studies”.

2.1.1.2 TNSG ON DOSSIER PREPARATION - DOCUMENT II-A

The TNsG on Preparation of Dossiers and Study Evaluation sets out the reporting format for the section dealing with the efficacy of the active substance for Document II-A in:

- Part I (*Dossier Preparation*)
- Appendix 5.1 (*Reporting format for Document II-A - Effects Assessment for the Active Substance*)
- Section 2 (*Effectiveness Against Target Organisms*)

Section 2.3 (*Effects on Target Organisms*) indicates that this section should include:

*Experimental data on the effectiveness of the active substance against target organisms
(See example table below)*

It is then followed by the sample table entitled *Experimental data on the effectiveness of the active substance against target organisms*, which includes columns to record information on

the test substance, test organism(s), test system / concentrations applied / exposure time, test results: effects, mode of action, resistance, and a column to record the reference in which this information can be found.

As the reporting format directs an Applicant to provide a summary of experimental data, the implication is that efficacy studies are required on the active substance.

2.1.1.3 TNSG ON DOSSIER PREPARATION - DOCUMENT III-A

The reporting format for the section on the efficacy of the active substance for Document III-A is set out in:

Part III (*Standard Formats*)
Section A5 (*Effectiveness against target organisms and intended uses*)

At the end of this section, a summary table titled *Section 5.3: Summary table of experimental data on the effectiveness of the active substance against target organisms at different fields of use envisaged, where applicable* is included.

The format of this table includes space for information on the function, field of use envisaged, test substance, test organism(s), test method, test conditions, test results: effects, mode of action, resistance, and again includes a column to record the reference in which this information can be found.

Again, the reporting format given in the TNsG directs an Applicant to provide a summary of experimental data, implying that efficacy studies are required on the active substance. However, the guidance does not include a Robust Study Summary format for submitting efficacy studies.

Therefore, we have the situation where the TNsG on Data Requirements and the TNsG on Dossier Preparation do not give consistent guidance as to whether efficacy data are required to support the active substance.

2.1.2 BIOCIDAL PRODUCTS

The situation is more straightforward for biocidal products, as the TNsG are in agreement that efficacy data are required to support the associated biocidal product.

2.1.2.1 TNSG ON DATA REQUIREMENTS

The TNsG on Data Requirements deals with the efficacy data requirements for biocidal products in:

Chapter 2 (*Common Core Data Set for Active Substances and Biocidal Products*)
Part B (*Common Core Data Set for (Chemical) Biocidal Products*)
Section 5 (*Intended Uses and Efficacy*)

Section 5.10 includes the requirement to submit efficacy data, and specifies:

The proposed label claims for the product and efficacy data to support these claims....

2.1.2.2 TNSG ON DOSSIER PREPARATION - DOCUMENT II-B

The TNsG on Preparation of Dossiers and Study Evaluation sets out the reporting format for the section on the efficacy of the active substance for Document II-B in:

Part I (*Dossier Preparation*)
Appendix 5.2 (*Reporting format for Document II-B - Effects and Exposure Assessment for the Biocidal Product*)

Section 7 covers *Efficacy*. Like the entry for Documents II-A and III-A, it includes a summary table for listing the efficacy data.

The format of this table includes space for information on the test substance, test organism(s), test system / concentration applied / exposure time, test conditions, test results: effects, mode of action, resistance, and includes a column to record the reference in which this information can be found.

Again, the reporting format directs an Applicant to provide a summary of experimental data, therefore agreeing with the data requirements that efficacy studies are required on the biocidal product.

2.1.2.3 TNSG ON DOSSIER PREPARATION - DOCUMENT III-A

The reporting format for the section on the efficacy of the biocidal product for Document III-B is set out in:

Part III (*Standard Formats*)
Section B5 (*Effectiveness against target organisms and intended uses*)

The format for Section B5, unlike those for Doc II-A, II-B, and III-A, does not include the requirement for a table summarising the efficacy data, despite the data requirements indicating that efficacy studies are required, and Doc II-B requiring a study of the data which should be present in this document..

2.1.3 CONCLUSION

It is concluded that the efficacy data requirements for active substances and biocidal products should be clarified in order to provide clear guidance to both Applicants and Member States.

2.2 EVALUATION AT ANNEX I INCLUSION STAGE

2.2.1 ACTIVE SUBSTANCE AT ANNEX I INCLUSION

Although an associated biocidal product is evaluated at the Annex I inclusion stage, this part of the BPD process is concerned primarily with active substances. The purpose of the review is to determine whether the *active substance* is suitable for inclusion on Annex I or not.

However, the efficacy of the active substance is not currently included in the evaluation carried out at the Annex I inclusion stage. The guidance on data requirements and document formatting indicate that efficacy data should be available on the active substance, although an evaluation of these data is not specifically called for.

Efficacy studies should be submitted on the active substance, and these data should be capable of demonstrating the innate activity of the active substance against representatives of the proposed target organisms.

It shall be noted that there is an important link between efficacy and the risk assessment for human health and the environment. The information on efficacy is relevant in assessing the dose recommended for the use(s) applied for. The dose (or the "likely concentration(s) at which the active substance will be used" as stated in Annex IIA V 5.3 of the Directive) is the starting point in the exposure assessment for human health and the environment.

Efficacy needs not be demonstrated against the full range of target organisms at this stage, as additional target organisms can be added at the Product Authorisation stage. In most cases, demonstrating efficacy against one target organism will be enough to recommend Annex I inclusion of the active substance, although there are situations where it will be desirable to have efficacy demonstrated against a wider range of targets (such as for active substances to be used in disinfectants, for example).

As the testing on an active substance is normally carried out using the technical active substance, or a simple dilution of the active substance in water or an appropriate solvent (so that the testing is carried out in the absence of other substances which may effect the efficacy), an extensive data package and evaluation should not be required at this stage

Additionally, the levels of efficacy demonstrated need not be high, as it is generally not intended that the active substance will be used in this way. An active substance in simple solution may not be as effective as one used in a fully formulated product, and so an active substance should still be considered suitable for Annex I inclusion even if the levels of Efficacy demonstrated are lower than these which would be expected for a formulated product.

Where the levels of effect noted are low enough to raise concerns with the evaluating Member State, the Applicant should be asked to defend why the levels of activity noted should be considered acceptable (such as, that high levels of activity should not be expected when the substance is in a simple formulation because of specific properties of the substance or matters related to its mode of action. This could include active substances tested in water, which would require the presence of emulsifiers to be more effective, for example).

2.2.1.1 CONCLUSION

It is concluded that efficacy data should be required on the active substance, to demonstrate the innate activity of the active substance (either the technical grade active substance or a dilution in water or a solvent) against one or more of the proposed target organisms.

2.2.2 BIOCIDAL PRODUCT AT ANNEX I INCLUSION

Although Annex I inclusion is concerned with active substances, efficacy data should also be required on the biocidal product in order to demonstrate that the active substance is capable of producing an effect on the target organism when included in a formulated product.

However, some Member States are of the opinion that a detailed evaluation of the effectiveness of the product (including an evaluation of the proposed label claims) is not appropriate at the Annex I inclusion stage.

There are several of reasons for this view, including:

1. There are a number of situations where the product that is included in the dossier for Annex I inclusion may not be representative of a real, in-use product (this is discussed more fully in section 2.2.3)
2. In the evaluations carried out so far for inclusion onto Annex I, there has not yet been a detailed evaluation of the label claims for a biocidal product during an evaluation for Annex I inclusion. In each case, this evaluation has been deferred to the Product Authorisation stage. It is proposed that this practice should continue to be followed in future, and should be formalised in order to ensure consistency of approach between dossiers.
3. Some Member States have encountered situations where the efficacy of a biocidal product (when evaluated at the Annex I inclusion stage) has not been demonstrated at a level which would be considered acceptable for a final marketed product. As efficacy is closely related to how a product is formulated, we think that it would be inappropriate to block Annex I inclusion of an *active substance* on the efficacy of a *biocidal product*, especially as reformulating the product may increase the efficacy.

In line with the principles discussed for the active substance in 2.2.1, efficacy should not need to be demonstrated against the full range of target organisms at Annex I inclusion, especially bearing in mind that additional target organisms can be added during the detailed evaluation at the Product Authorisation stage.

2.2.2.1 PROPOSAL

It is proposed that the efficacy data required for the biocidal product at Annex I should be suitable to demonstrate that the active substance is capable of producing an effect on one or more of the proposed target organisms when formulated into a product.

Annex I inclusion should still be recommended where the efficacy data are suitable to demonstrate that the active substance (when included in a formulated product) is capable of producing an effect against the target organisms, even where the levels of efficacy demonstrated would not be considered adequate for a product at Product Authorisation.

As with the active substance in Section 2.2.1, where the levels of effect noted are low enough to raise concerns with the evaluating Member State, the Applicant should be asked to defend why the levels of activity noted are considered acceptable for Annex I inclusion (for example, a dummy formulation has been used).

This will help active substances to gain Annex I inclusion, whilst allowing the product to be reformulated or undergo further testing in order to generate an adequate efficacy data package for Product Authorisation.

A detailed evaluation of the efficacy of a biocidal product and its label claims should not be carried out at Annex I inclusion, but rather at the Product Authorisation stage.

This will also ensure consistency with previous evaluations, where the major assessment of efficacy has been deferred to the Product Authorisation stage.

2.2.3 SITUATIONS INVOLVING “UNREALISTIC” PRODUCTS

Some of the associated biocidal products which are included in a dossier submitted for Annex I inclusion may not adequately represent those biocidal products which will finally be placed on the market.

2.2.3.1 “DUMMY PRODUCTS”

A dossier for Annex I inclusion of an active substance may be accompanied by a “dummy product” as the associated biocidal product.

A “dummy product” is normally one which is not a fully formulated product intended for final sale, but instead has been included in order to satisfy the requirement to provide a biocidal product to accompany the active substance dossier.

This type of product may be included where the Applicant has little experience of formulating products, such as Applicants who only manufacture active substances. While some dummy products may be close to a fully formulated product, others may be a very simple formulation that bears little relation to the products which will finally be placed on the market.

As dummy products are not formulated like a normal end use product, this can lead to problems for the Applicant in generating a comprehensive efficacy package, as the dummy may not be as effective as a correctly formulated product. A dummy product is also unlikely to have a full set of detailed label claims, against which the efficacy of a product should be assessed.

It may therefore not be possible to carry out a detailed assessment of the efficacy of a dummy product.

2.2.3.1.1 PROPOSAL

It is proposed that only a minimal evaluation of product efficacy data be carried out at Annex I inclusion. This evaluation should be able to demonstrate that the active substance is capable of producing an effect when formulated into a product. A full evaluation of efficacy should instead be carried out at the Product Authorisation stage.

This will allow the active substance to gain Annex I inclusion, and mean that the efficacy of dummy products will not be subject to the same degree of scrutiny as that of properly formulated products. As a full assessment of efficacy will be required at Product

Authorisation, all products which are intended to be placed on the market will be subject to a detailed efficacy assessment, while dummy products (which are not intended to be placed on the market) will not be.

2.2.3.2 ACTIVE SUBSTANCES WHICH ARE NOT INTENDED TO BE USED IN ISOLATION

Problems may also arise where the active substance being evaluated is not intended to be used as the sole active substance in a product. This can occur in situations such as when an active substance has a limited, rather than broad based, spectrum of activity.

For example, a fungicidal active substance for use in wood preservation may provide good activity against Ascomycete fungi, but be less effective against Basidiomycetes. In this example, the active substance may be used in conjunction with a different active substance (one which is more efficacious against Basidiomycete fungi) in order to control both types of fungi.

While it is simple to produce efficacy data to support the active substance for the purposes of Documents II-A and III-A, how should efficacy data on the product be addressed?

If a formulation is tested which contains only the single active substance under review, then this is not representative of the final product (which will contain another active), and is more in the nature of a dummy product. If this formulation were to be tested and evaluated in line with the label claims for the product, then it would not be able to produce the results claimed for the end use product (as the claims would describe the activity of the product containing multiple active substances). For example, testing may only have been carried out against a restricted range of target organisms.

However, if a formulation containing two or more active substances were to be tested, then the contribution of the active substance being evaluated could not be determined. Any activity shown by the formulation could be as a result of the other active substances.

Whilst the efficacy of the whole product can be demonstrated, this does not provide evidence that the active substance is capable of working in a formulated product (data of this type would be suitable to support the product at the Product Authorisation stage, however).

2.2.3.2.1 CONCLUSION

It is concluded that only a minimal evaluation of product efficacy data is carried out at Annex I inclusion. This evaluation should be able to demonstrate that the active substance is capable of producing an effect when formulated into a product.

A full evaluation of efficacy should be carried out at Product Authorisation, where the efficacy of the formulated product (containing multiple active substances) can be assessed and compared to the label claims.

2.3 ASSESSMENT OF LABEL CLAIMS

2.3.1 DEFINITION OF “LABEL CLAIMS”

The TNsG on Data Requirements include as one of the data requirements for biocidal products; “The proposed label claims for the product and efficacy data to support these claims....”

The label claims should be included in Document III-B Section B5.10.1, and a copy of the product label should also be in the dossier. However, the claims given in this section and on the label often do not give a clear indication of the intended uses of the product - in other words a detailed listing of target pests, any claims for residual action or speed of effect, or other specific use claims, and this information may not be present on the label at all.

This is particularly true for professional products, which tend to have much shorter labels that concentrate on safety issues, rather than for amateur use products, which may contain label claims intended to help sell the product by pointing out its benefits.

For example, the label provided for the biocidal product accompanying a dossier on an active substance for use in PT 12 (slimicides) did not contain any claims other than describing the product as a “microbicide”.

The label itself did not describe the target organisms it was intended for use against or the effects of using the products (such as “for the control of anaerobic and sulphate reducing bacteria in water systems”). In fact, in the case of acrolein, the product was being used as a “corrosion inhibitor”, which is not a biocidal claim in itself (it prevented corrosion by killing the anaerobic and sulphate reducing bacteria which cause the corrosion). Therefore, there were no “label claims” on the label itself, against which an efficacy assessment could be conducted.

However, it is reasonable to assume that this information is present elsewhere, in order to inform potential purchasers of the benefits of the product. This information may be available on accompanying information (such as leaflets) or on advertising material.

This information should also be considered as part of the claims made for a biocidal product. Article 20 of the BPD already regards certain information on accompanying leaflets as being part of the label information.

2.3.1.1 CONCLUSION

It is concluded that the term “label claims” be interpreted to include all claims made for the efficacy of the product, such as those on advertising material or accompanying leaflets, as well as those on the product label.

2.3.2 EVALUATION OF LABEL CLAIMS AT ANNEX I INCLUSION

In the evaluations carried out so far for inclusion onto Annex I, there has not been a detailed evaluation of the efficacy data submitted compared with label claims for the biocidal product.

In fact, the TNsG on Preparation of Dossiers and Study Evaluation do not include entries or space in Documents II-B or III-B for an evaluation of label claims, which may explain why this has not been carried out.

2.3.2.1 PROPOSAL

It is proposed that a detailed evaluation of the efficacy data against the label claims be carried out at the Product Authorisation stage, and not at the Annex I inclusion stage, which is more concerned with the active substance.

This approach would be consistent with previous evaluations, where the assessment of product efficacy has been deferred to the Product Authorisation Stage.

2.3.3 EVALUATION AT PRODUCT AUTHORISATION STAGE

The Product Authorisation stage is the point in the evaluation process where the efficacy of the biocidal product should be looked at in detail.

At this stage, it is not the properties of the active substance which are of interest, but instead the properties of the fully formulated product, which may contain more than one active substance.

Therefore, this is the stage at which a detailed evaluation of the efficacy of the formulated product should be carried out, and where the efficacy is evaluated in relation to the label claims made for the product.

This evaluation should include all relevant target species (or representative species), the effects of using the product, the duration and speed of effect, any claims for residual action, together with any other specific claims.

2.3.3.1 CONCLUSION

It is concluded that detailed evaluation of the efficacy of a biocidal product and its label claims should be carried out at the Product Authorisation stage.

3 SUMMARY OF PROPOSALS

It is concluded that:

- 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.
- 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.
- 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 an acceptable justification, Annex I inclusion should still be recommended and the efficacy more fully addressed at the Product Authorisation stage.
- 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.
- As only a minimal evaluation of efficacy takes place at the Annex I inclusion stage, a comprehensive efficacy evaluation should be carried out at Product Authorisation.
- 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.