Miljøministeriet
Miljøstyrelsen

Guide to efficacy studies

Below is a brief presentation of the requirements that must be met in order to have a biocide for deterrence of mammals (PT19) assessed for efficacy with a positive result. The guide also includes a description of the more general requirements for efficacy studies.

The text refers to a technical note on guidance from ECHA regarding practical procedures concerning authorisation and registration of biocide products. Especially chapter 7 and appendices to chapter 7 are relevant (TNsG). This appendix describes in detail the requirements regarding efficacy studies and explains these requirements for the individual species or groups of species. However, no specific guidance is given for efficacy studies on deterrents for mammals (product type 19), but the guidance for studies of rodenticides thoroughly explains the general principles for experiments on mammals under standardised and natural conditions (cf. p. 171-181). TNsG can be accessed here: http://echa.europa.eu/documents/10162/16960215/bpd_guid_tnsg-product-evaluation_en.pdf

Definition of a deterrent – product type 19

This guidance is directed towards companies that need to provide documentation for the effect of the product as part of the product promotion of a biocide as a deterrent for mammals.

The general definition of a deterrent is a product for: deterring of annoying or harmful organisms like insects, birds and mammals including products that are directly or indirectly used for protection of farm animals, pets and humans against harmful organisms.

This guidance specifically concerns deterrents used for controlling mammals by deterring these from either a physical site, where the animal is unwanted, or from a resource to which the animal causes damage. Examples of mechanisms of action for biocide deterrents include:

- Smell, which deters the animals
- Ugly taste, which keeps the animal from eating foods treated with the biocide
- Pain induction/discomfort, e.g. stomach ache, by which the animal associates the discomfort with for example the food and thus stops eating this food
- Chemical irritation of the skin or senses (e.g. capsaicin).

A deterrent agent is a biocidal product, unless the purpose of deterrence is to protect plants or for use on cultivated areas. In the latter case, then the deterrent is regarded a pesticide. This guide (or an authorisation of a deterrent biocidal product) does not contravene the rules on the protection and conservation of plant and animal species in the Danish Nature Protection Act and the Hunting and Wildlife Administration Act.

Active ingredient or product?

Applicants seeking authorisation have to be aware that it is the entire **finished product** and its **directions for use** that are up for approval and not only the active ingredient contained in the product. Usually, the active ingredient in itself is well known, and its effects on the relevant animals are known. (This is however not always the case, as the active substances on Annex I, where applying through the simplified procedure is possible, have not undergone efficacy evaluation.) What is to be assessed is the entire, formulated product with its final chemical composition in the packaging and with the directions for use under which it is to be made available on the market. The product must live up to all points mentioned in the directions for use.

Below are outlined some possible pitfalls:

Example 1:
An enterprise applies for approval of a deterrent for cats but has only used female cats when testing the efficacy of the product. The effect on male cats is very poor, and in practice, the product will not have any effect on these.

Example 2:
An enterprise applies for approval of a deterrent for beech martens but has only tested the effect the first days after laying out the product. It turns out that beech martens quickly get used to the product, after which the product is no longer effective as a deterrent.

Example 3:
An enterprise applies for approval of a deterrent, which is to keep herbivores from damaging crops by inducing stomach ache when the animals eat the crop. It turns out that the product is poisonous to some of the other species in the biotopes where the crop is grown, thus the products does not only deter but also kills the animals in question.

Directions for use

The directions for use form the very basis of the efficacy assessment. What is printed here determines the requirements regarding the necessary documentation. Therefore, there is a good deal of information, which both the user and those assessing the efficacy must be able to get by reading the directions for use. The directions for use must be described in the SPC of the application.

"Normal use" and "conditions for the approval"
The directions for use are always assessed compared with what is considered normal use and in accordance with the conditions that may be imposed on the product.

Thus, the applicant must consider what ”normal” use is as well as consider the ”conditions for the approval” by answering the following 5 points in relation to the product in question:

1. Which type of product and formulation is it?
    - Spray, ULV (ultra low volume) product, powder, aerosol etc.

2. Method of application?
    - Surface treatment (applied with a brush, low-pressure spray equipment, etc.)
    - Treatment of specific, small areas
    - Laying out
    - Powdering
    - Evaporation
    - Treatment of a product, which the animal eats, e.g. crop or stock goods

3. Dose rate?
   Here the applicant must indicate the dose rate of the product. Sometimes, this causes difficulties because treatments with products for use outdoor, in dwellings or food producing facilities should not always be carried out homogeneously. Nevertheless, a dose rate must be given. The dose rate is a precondition for the consumer's use of the product and to the assessment of the submitted efficacy data.
   Examples of dose rates can be:
    - Volume per m^2
    - Volume per m^3
    - Gram per m^2
    - Spray for ”a number of” seconds per linear metre
    - Distance between dispensers
    - Number of units/dispensers per area or metre

4. Does the treatment need to be repeated?
   Some products require repeated treatments; in those cases it must appear from the directions for use how and how often.

5. Other things?
   These may be preconditions which must be met, such as:
    - The surroundings must have been cleaned
    - The product is to be used together with another product
    - The product is to form part of a broader control strategy for deterring
    - Avoiding the use of hot water after treatment
    - Avoiding treatment in places where farm animal or pets can lick, stay or be in contact with the product
    - The product must be placed inaccessible for children

What does the product do and what is the advantage of using it?
It must appear from the directions for use which specific animals or groups of animals you want to deter with the product. Here you have two options:

1. Stating precisely which mammal (species) you intend to control with the product, for example beech martens, including the species' name in Latin.

In this case you must present efficacy data for the animal species you wish to mention.

2. Stating several specific species which you intend to control, for example beech martens and a specific species of bat. In this case you must present efficacy data for each species listed. Further, animals may be mentioned in general terms, for example *grazing animals, predators* or *rodents*.
   Here the applicant must present documentation for specific representative species as you cannot provide documentation for all grazing animals, predators or rodents. The choice of representative species may vary according to what you wish to write in the directions for use. However, studies of other relevant species may also be considered during the evaluation.
   The applicant need to be aware that if specific species are added to these otherwise general products, documentation for the species mentioned must be presented. If, for example, ”in corn fields” to “grazing animals” are added, the applicant must also present studies of relevant mammals in a corn field.

If, for example, you claim in the directions for use that the product ”is effective instantly after laying” or “has a certain long-term effect”, you must also provide documentation for these claims meaning that you also have to describe the temporal effect.
Furthermore, you must examine how the product affects species that unintendedly are subject for the product, meaning species living in the same area as the species you wish to deter.

At which level do you achieve an effect by using the product?

1. Effect at individual level:
   The product deters the animals that have been in direct contact with the product. Therefore, individuals with yet no experience with the product will not be deterred.

   Example:
   A product for deterrence of beech martens is laid out on an attic, where the presence of a beech marten has been determined. This individual will be deterred, but after a short time, a new beech marten, with yet no experience with the deterrent, will move in.

2. Temporal effect:
   The effect of the product will decrease over time, as the animals get used to the product. This will often be the case if the product does not have negative consequences for the animal except from being deterred to begin with.

   Example:
   You treat your garden with a product deterring cats from entering the garden. The cats learn that besides from smelling unpleasantly the product does not have any negative consequences, and after some time they begin to enter the garden again. Often, cats’ motivation for staying in an area will be affected by the size of the population in the given area, and the more cats in the area, the stronger their motivation for entering areas where a deterrent is used.

The efficacy assessment

What documentation can be used for an efficacy assessment?
Studies included in the efficacy assessment must substantiate the effect that is described in the directions for use. Not many specific guidelines cover the target group of the mammals and uses included in the notes for guidance on efficacy assessments (product type 19). The use of specific guidelines is therefore not a precondition to a study being included in the evaluation. However, the studies must live up to some basic requirements (see below: Requirements regarding the quality of efficacy data). All studies, published or non-published, will be assessed on the basis of their contents, and they will not be rejected for technical reasons. However, one precondition is that methods and results are described in such detail that the study can be repeated on the basis of this description.

Documentation in the form of descriptions of what one or more persons have experienced when using the product cannot be used in connection with an efficacy assessment. Thus, studies based on praise from private persons, companies or others (competent professional individuals, experts etc.) and not followed up by a concrete, well-documented data material will not be included in the efficacy assessment.

Which types of studies must be presented?
In TNsG, the relevant types of studies that are to be carried out in order to provide documentation for the efficacy of the product are considered.

1. Laboratory studies (screening)
2. Simulating studies
3. Field studies.

Re 1 laboratory studies:
By using laboratory studies you can examine how individuals from the species in questions react to the active ingredient in the product. It is basic studies on whether the species is capable of sensing the biocide, dose response studies, studies on sexual differences, age differences and whether the ingredient affects the animal harmfully. However, it is important to emphasize that the reactions you see in surroundings unnatural to the animal not necessarily can be compared to the reaction under natural conditions.

Laboratory studies will not always be possible for species that cannot be kept in captivity without being stressed. Besides affecting the animals' welfare, stress due to captivity will result in non-usable data. However, this type of study will be obvious for products for domestic animals and pets like dog and cat, or in cases where you can find domesticated animals of the species in question.

Re 2 simulation studies:
In simulating studies, the finished formulated product will be tested with the correct concentration and with the recommended use in controlled surroundings where you try to create the conditions under which the product will be used by the users. The same problems as with the laboratory studies can be seen here in relation to wild animals' response to artificial surroundings.

Re 3 field studies:
Field studies mean studies carried out with the product applied for in the places in which the finished product is to be used, such as private dwellings, stables, grain stores, gardens, areas of crop production etc.

Optimally, all three types of studies should be included in the documentation material. However, laboratory studies including wild animals can be omitted if these studies cannot be carried out with sufficient profit as described above. Simulated tests may be dispensed with if several good field studies are available. All tests must be carried out with the animals which you claim that the product is effective against.

Requirements regarding the quality of efficacy data
The documentation for the efficacy of a product must comply with the general requirements to be met by scientific studies regarding data collection, statistical treatment as well as reporting.

The list below states which information must be available in a report, no matter which experiment you intend to report. Furthermore, you can see more in the table on page 110 in TNsG.

- Name and concentration of the active ingredients included in the study.
- If tests are performed on several versions of the product, it must be clearly stated which of the tested products is identical to the product that is being evaluated. If the tested product differs from the product applied for, the composition of the tested product must be stated so that it is possible to assess whether the results can be used as documentation for the efficacy of the product for which approval is sought.
- The purpose of the study must appear as well as what will be determined through the study.
- A detailed description of the experimental conditions – season, temperature, relative humidity, light conditions, research animals' access to feed and water, their access to conspecifics, the layout of the trial site (this may for example be a cage or an entire stable), the area and geographical location of the site and other relevant conditions.
- Description of the test animals used
    - Have the animals become acclimatised before the trial and how?
    - How many test animals are involved in the trial?
    - The group of test animals must be thoroughly described regarding homogeneity and relevance for the use of the applied product. Are the test animals adults? Are both sexes represented? How old are they? Are they fasting or have they been fed, and in the latter case with what and how much? Where do the test animals come from, and what is their history (caught in the wild or reared in a laboratory?) etc.
    - Do the test animals have previous experience with the active ingredient?
    - Are you testing a particularly susceptible population?
- Trial design
    - You must describe the study's trial design.
    - A control experiment without any active ingredient but with exactly the same set-up and the same extent must always be presented (negative control). In some cases a positive control is

also used in which the product applied for is measured against a comparable, but well-described product. Such treatments cannot replace a negative control treatment.
    - How many replications are used in the experiment?
    - How many individuals does a replication consist of?
    - What considerations are behind the choice of the number of animals and replications, and which precision can you therefore expect from the study (the power of the study)?
    - To what extent are the replications independent of each other, and how will a lack of independence between the replications, if any, affect the result?

- In field trials replicates are rarely real replicates. Instead you have to carry out your experiments at a number of sites which resemble each other as much as possible. In such a situation you must report the size of the population in question before and after the treatment. A very detailed description of the experimental conditions is generally required when field studies are reported.
- A detailed description of the method used for data collection, e.g. a description of systematic behavioural observations.
- The duration of the study including the duration of the individual data collection periods must be presented.
- Which outcome measures used and a thorough description and argumentation for the choice of these.
- When ingredients that are added to animal feed are tested, the following questions must be discussed:

    - Is alternative food available during the experiment? Can the test animals for example find their normal food in the surroundings, or are they offered a non-treated alternative, or are they offered a competing product?
    - If you measure the amount of food intake, a covered-up reference food must also be included in the trial experiment in order to correct for drying/absorption of moisture.
- Raw data must always be enclosed.
    - Data are presented in the actual report in relevant calculations and tables, but data in their raw form must also be available – preferably in an appendix
    - Raw data mean the data collected during the experiment before calculation.
    - All data must be present in the report, both the data of the product applied for and of the untreated control.
- If the report contains references to guidelines, then these guidelines must be enclosed in full.
- The statistical methods used must be reported.

The worst pitfalls

- The results have been reported in the form of percentages without the raw data being enclosed.

- In the case of broad-spectrum products the experiments were carried out with species not representative of the use of the product that is stated on the label.
- Not the same number of untreated control experiments was carried out as the number of experiments with the product.
- A number of national guidelines are being referred to without these being enclosed, and without information about how the current experiment differs from those guidelines.
- Letters, popular articles and other material from highly satisfied customers are enclosed as documentation – this cannot form part of the documentation for the product.
- Papers from internationally recognised scientific journals are enclosed, documenting that the active ingredient is effective or that a number of named products are effective. This can only be used as documentation if the product applied for – that is precisely the formulation applied for – was studied in the paper in question.
- In recent years, directions for use have appeared to have clearly been translated by online translation services. These are often almost unintelligible and mention species names that do not exist in Danish. Such texts cannot form the basis of an efficacy assessment and will obviously pose a risk of stopping the entire evaluation process.
- The use of local names for animals in the target group may be necessary and acceptable; however, it cannot be used if there is a risk that it will result in misunderstandings. In all cases, the Latin name of the animal in question should appear in the directions for use.