

**GUIDANCE ON THE STORAGE STABILITY
DATA REQUIREMENTS FOR NON-
AGRICULTURAL PESTICIDE PRODUCTS**

CONTENTS

1. INTRODUCTION

Background	Page 2
New guidance document	Page 2
Why storage stability data are needed	Page 3
When storage stability data are required	Page 3

2. DATA REQUIREMENTS

Accelerated storage stability studies	Page 4
Ambient (two year) storage stability studies	Page 5
Cold stability testing	Page 6
Reactivity towards container material	Page 6

3. GUIDANCE ON STORAGE STABILITY DATA REPORTING

General points	Page 7
Good Laboratory Practice (GLP)	Page 7
Type of stability test conducted	Page 8
Product name	Page 8
HSE number	Page 8
Packaging	Page 8
Pack size	Page 8
Visual inspection	Page 8
Temperature	Page 9
Time	Page 9
Batch numbers	Page 9
Analytical methods	Page 9
Test data	Page 9
Calculations	Page 10
Conclusions / discussion	Page 10
References	Page 10
Appendices	Page 10

4. APPENDIX

(Guidance on preparing reasoned case letters)	Page 11
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5. REFERENCES Page 13

6. GLOSSARY OF TERMS Page 14

1. INTRODUCTION

Non-agricultural pesticides are presently regulated in Great Britain under The Control of Pesticides Regulations (COPR) 1986, as amended, and require approval before they can be sold, supplied, stored, used or advertised. The term non-agricultural pesticide covers wood preservatives, wood treatment products, biocidal paints, surface biocides, rodenticides and insecticides/acaricides for use in public hygiene situations, avicides, bird stupefying baits and antifouling products.

This guidance document is one of a series of documents that has been developed by HSE's Biocides and Pesticides Assessment Unit to support the approval of non-agricultural pesticides under COPR.

Background

Following agreement of the Advisory Committee of Pesticides, the HSE produced a guidance document "Data requirements for non-agricultural pesticides products and their active substances" (found in Part Three/A of the Registration Handbook). The requirements published in July 1993 establish a consolidated (core) set of data requirements for all non-agricultural pesticides.

The core data requirements apply to the registration of a pesticide containing a novel active ingredient but also are used to support the review of older active ingredients and their products.

New guidance document

The purpose of this guidance document is to amplify the core data (chemistry) requirement for "stability during storage" set for formulated products.

Requirements may be waived for some elements of the data outlined in this guidance if, on a case-by-case basis, the applicant can provide an acceptable written rationale based on sound scientific reasoning. Further advice on the preparation of reasoned cases is given in the Pesticides Newsletter No.38, March 1998 (see *appendix*).

This document provides generic guidance in this area for the current spectrum of non-agricultural pesticide products under COPR and should be read in conjunction with the 1993 guidelines on core data requirements.

N.B. Specific guidance for rodenticide products with regard to addressing "storage effects and efficacy" is given in the Efficacy Guidelines for rodenticides, which is available on BPU's website.

This guidance document is also available on BPU's website:

<http://www.hse.gov.uk/hthdir/noframes/bpau.htm>

Why storage stability data are needed

Information on the physical and chemical characteristics of a product is directly used in hazard assessment.

The purpose of storage stability testing is to provide evidence on how the quality of a product varies with time under the influence of environmental factors such as temperature, humidity and light. The evidence provided by such studies will give an indication of the effect these factors may have on product quality, safety and performance (efficacy). The main objective of testing being to determine how long the product will retain the percent active ingredient in its packaging.

Storage stability studies provide data on change (or lack of change) in product composition over time. If certain ingredients decompose under conditions of high (or low) temperature and humidity, then other new chemicals may be formed whose toxicity may need to be considered. The results are used to establish storage conditions and determine a suitable shelf life for the product¹.

Additionally, pesticide containers have an important effect on storage and shelf life. If the product is corrosive then lids, liners, seals, seams or container sides may be damaged over time causing the contents to leak during storage, transportation, handling or use. Labels may also become illegible or damaged. In such instances the corrosion characteristics of a pesticide will be needed to evaluate the effects of the product formulation on the container.

When storage stability data are required

Data to demonstrate “stability during storage” are required for pesticidal products in support of the registration of a new active ingredient but may also be required to support the review of older existing active ingredients and their products.

¹ This requirement is increasingly being set as a post review data requirement by the Advisory Committee on Pesticides (ACP). Although not specified in the Core data requirements for non-agricultural pesticides additional requirements examining the technical properties of a non-agricultural pesticide formulation (e.g. emulsion stability, wettability, suspensibility, friability etc) as appropriate may also be requested by the ACP following a review of an existing active ingredient and its products

2. DATA REQUIREMENTS

In order to fully characterise the stability of a pesticide formulation, standard test methods may be used. Subjective judgement and/or familiarity with the formulation and its intended use are needed in selecting the appropriate test(s).

The test requirement for stability during storage can normally be established in one or more of the following ways:

- accelerated testing (provisional approval only)
- ambient testing
- cold stability testing
- testing for reactivity towards container material

Accelerated storage stability studies

An accelerated study is used to indicate the ageing of a product by elevated temperatures. The currently preferred method for accelerated storage stability is the Collaborative International Pesticides Analytical Council (CIPAC) MT 46.3: accelerated storage procedure.

The CIPAC method studies samples stored at 54 °C over a period of 2 weeks (unless other temperatures and times are specified in the FAO specifications for particular formulation types).

For preparations unstable at these temperatures alternative times and temperature regimes are available (e.g. 4 weeks at 50 °C; 6 weeks at 45 °C; 8 weeks at 40 °C; 12 weeks at 35 °C; 18 weeks at 30 °C). If, for example testing shows that:

- significant loss of active has occurred due to reactions at this elevated temperature, and
- storage conditions are not realistic of how the product will be stored (*i.e.* UK/French climate)

Samples should be analysed before and after testing using the same batch. The packaging should be based upon that in which the product is sold and the packaging used in the study should be assessed for any interaction with the formulation.

Data provided from an accelerated study can give a useful indication of a products stability but it should be noted that products may also pass this test and yet still be unsatisfactory in the field. For this reason storage stability data generated from accelerated tests will only support provisional approval. Data from storage at ambient temperatures must be provided to support full approval under COPR.

N.B. Accelerated storage stability studies can only be used to support provisional approval for non-agricultural pesticide products.

Two-year storage stability studies (Ambient testing)

This is used to demonstrate the storage stability of a formulation under “true” storage conditions usually over a period of 2 years, i.e. representative of its expected shelf life under normal use.

The tests should be conducted at ambient temperature or, 20 °C, 25 °C or 30 °C dependent on the final area of use.

Ambient temperatures must reflect the maximum and minimum temperatures likely to be experienced (for example, a warehouse, garden shed, kitchen sink etc.). As a general rule of thumb, a sample stored in an unheated warehouse would encompass a range of expected storage conditions.

Data on temperature and humidity should be reported as part of the study (for example mean monthly temperatures and extremes of temperature).

Samples should be analysed before (initial analysis at the start of the trial) and after testing using the same batch. For long-term studies, intermediate analysis (3 and 6 months) should be carried out also. The packaging should be based upon that in which the product is sold and the packaging used in the study should be assessed for interaction of the formulation.

Acceptable variations in active ingredient content will depend on the initial active ingredient content in the formulation.

The following variations are adapted from the "Manual for the Development of FAO and WHO Specifications for Pesticides" (First Edition):

% Active ingredient content	Acceptable variation in active content (%)
<2.5	±15
2.5-10	±10
10-25	±6
25-50	±5
>50	±2.5

Variations (after 2 years at ambient temperature storage) outside those listed in the table above will deem the formulation to have failed the storage stability test.

A two-year storage stability study is required in support of full-approval for non-agricultural pesticidal products under COPR. Due to the fact that the time from commencement of the study to submission to BPU can be up to 3 years, it is not feasible to repeat a study that has been considered unsatisfactory. It is therefore important that the protocol is agreed with BPU before commencement of the study.

Cold Stability testing

The aim of such a test is to ensure that the properties of formulations are not adversely affected by storage during periods of extreme cold.

If a product is intended to be stored under refrigerated conditions and/or it is considered that the active substance or preparation may crystallise, or where phase separation could occur, a cold stability test should be carried out at a temperature of 0 °C or lower.

CIPAC MT 39.3 (Stability of liquid formulations at 0°C) is the preferred method for formulations consisting of a solution of a pesticide in water or organic solvent (e.g. solution concentrates and emulsifiable concentrates).

Reactivity towards container material

Data regarding stability to metal and metal ions is normally required only if the product is corrosive and contact with metals during storage or use is likely.

Data are not required if an explanation regarding lack of corrosivity is submitted and considered acceptable (e.g. lack of extreme pH or alternatively, if information from experience in use and/or chemical structure indicate that testing is unnecessary).

N.B. A study of the storage stability of a product may be performed in combination with a study on the reactivity of the product to the container material.

3. GUIDANCE ON STORAGE STABILITY DATA REPORTING

General Points

For a critical scientific assessment of these data to be undertaken, each study must be reported in sufficient detail. The methodology used in each test must be thoroughly described, or if the study has been conducted to an internationally recognised protocol without significant deviation then a reference to this method will be sufficient.

The following paragraphs are intended to provide guidance on the extent and quality of the information required in a test report.

Good Laboratory Practice (GLP)

Good Laboratory Practice (GLP) is concerned with the organisational process and the conditions under which studies are planned, performed, monitored, recorded and reported. The regulations are not concerned with the interpretation and evaluation of test results. The EC Directive 87/18/EEC required member States to take all measures necessary to ensure that safety studies submitted to regulatory authorities in support of notification or registration of certain classes of chemicals were in accordance with GLP. With regard to the position of COPR the following points are relevant.

COPR does not make reference to GLP since it predates Directive 87/18/EEC and the UK GLP regulations. However, with respect to the principles of GLP and its applicability to the current statutory scheme for pesticides, the following arrangements were drawn up following a consultation exercise with Approval Holders and interested parties (Pesticides Newsletter, September 1992 and the Pesticide Register Issue 3, 1992 refer)

- (i) Mammalian toxicology studies started after 30th June 1988 must be carried out in compliance with the principles of GLP
- (ii) Physico-chemical studies and ecotoxicology studies after 1st January 1993 must be carried out in compliance with the principles of GLP
- (iii) All other safety studies started after 1st January 1993 must be carried out in compliance with the principles of GLP

Conditions (i), (ii) and (iii) apply to studies submitted either in support of an application for approval under COPR; or to satisfy a requirement for new data arising out of a review of a pesticide active ingredient or co-formulant.

With regard to the generation of product storage stability data, although it is not a requirement to store the product under GLP conditions, the analysis for the active ingredient must ALWAYS be conducted in compliance with the principles of GLP. For this reason a GLP compliant report must be submitted to address product storage stability for all studies that commenced after 30 September 2004 otherwise the study will be deemed unacceptable.

With respect to the provision of data on the technical properties and characteristics of a pesticide formulation GLP will be required for those studies that investigate potential hazardous properties (e.g. particle size, explosivity, flash point etc.) but will not be required for others where they do not impact on safety (e.g. colour, odour, emulsion stability, suspensibility, wettability, friability etc.)

Type of storage stability test conducted

The report should clearly indicate what type of storage stability test has been conducted on the formulated product (e.g. ambient, accelerated, cold etc.). The available data should contain a full description of test procedures and conditions, e.g. study duration, temperature etc.

Product name:

The product name should be stated clearly in the test report.

HSE number:

The HSE number (only if product is already approved) should be provided in the test report.

BPU accepts that certain products are sold as part of a range or family of similar products. Certain paints, for example, may differ only in colour; other products types may differ only very slightly in formulation. BPU will accept a storage stability study for a range of products if there is a justification provided with the report. A sample should be selected which is deemed representative of the entire product range.

Packaging :

The type of container (can, spray, bottle, sachet, etc.) and container material (metal, plastic, etc.) used in the study should either be the same as the commercial product or smaller packages of the same construction and materials. If the test product is to be supplied in different packaging, each type should be represented in the study.

Pack size:

The pack size and approximate empty weight or volume should be specified. These packs should be retained for the duration of the study to enable a visual comparison to be made with test product.

Visual inspection:

A visual inspection should be made of the packaged product at beginning and end of the study to determine any obvious signs of package failure or deterioration. In some cases it may be necessary to cut open packages at the end of the trial for an internal inspection for signs of corrosion or other reaction.

A visual inspection of the product should be reported and compared to a fresh sample. Any changes in colour, odour or clarity of texture of the product should be reported.

If the product label indicates that the product should be shaken before use, it is recommended that test samples should also be shaken prior to sampling. This may

be particularly important for viscous products that may be prone to settling, layering or stratification over the 2-year study.

Temperature:

The study should be conducted at the normal storage temperature expected for the product. If the product is intended to be stored under refrigerated conditions then the trial should also be conducted under the same conditions. If there is no specified storage temperature the study can proceed under normal temperature variations. The temperature and humidity should be recorded at regular intervals and presented in the test report. It is recommended that either the average monthly temperature and humidity are reported, or that monthly maximum/minimum values are recorded.

Time:

Samples are usually taken at 3 monthly, 6 monthly and 24 monthly intervals for ambient testing. The time (in weeks) at sampling should be recorded. Additional sample times can be added if necessary. The actual dates (in dd/mm/yy) of sampling need not be recorded.

Batch numbers:

If batch numbers are available, these should be included in the study report. A single batch trial is acceptable. The same batch sample should be used for the duration of the study.

Analytical methods:

If the study is submitted as part of a data package that already includes a validated analytical method of analysis for the active ingredient, this particular method should be used for the storage stability study. No further validation of this method would be necessary. Full method details should be provided in the study report. BPU has produced guidelines on method validation to clarify this issue.

Test data:

All test data should be reported. A table of the following information is very useful as a summary. Any table should include the following data:

- product name
- batch number
- temperature
- initial total mass (product + packaging)
- mass at sampling (product + packaging)
- mass change (%)
- product appearance
- container appearance
- active ingredients (%)
- change in active ingredient (%)
- any relevant comments
- results/interpretation
- tables and figures (where appropriate)

Calculations

Any relevant calculations should be included in the report. All calculations used to determine the amount of active substance should be clearly presented.

Conclusion/discussion

A general statement as to the suitability of the product and packaging should be made. Any significant changes in composition appearance or pack integrity should be discussed.

References

References to published or other public domain information should be included in the main text of the report. References should be complete with titles.

Appendices.

The test report should include at least one representative chromatogram from the analytical method. Chromatograms and any other relevant test data can be added as appendices to the test report.

APPENDIX

Advice on preparing a reasoned case – article taken from HSE Pesticides Newsletter, No 38, March 1998,

When Ministers grant approval for the use of a new active ingredient, they sometimes require additional data to be provided within a fixed deadline as a condition of approval. Similarly, the review of an existing active ingredient may result in approval holders being required to provide further data. Whenever data requirements are set, you may choose to provide a reasoned case arguing why you believe it should not be necessary to generate new data. This article provides some basic advice on what you should include in reasoned cases, and how you should present them.

Always contact the Biocides and Pesticides Assessment Unit (BPAU) to discuss your particular reasoned case in detail before you begin work.

Remember that the onus is on you to make your case for not generating new data. You should base your case on scientific arguments or other information, which demonstrates that the generation of new data is unnecessary. We understand that you may wish to comment briefly on the commercial implications, but do not use commercial concerns as the basis for your case.

There are various grounds on which to base a case against generating the specified new data. For instance,

- the outcome of a study may be predicted from existing data on the substance;
- existing data on one substance may be read across to fulfil a data requirement for another;
- a data requirement is not scientifically justified (for example, the use pattern indicates that such information is not needed);
- alternative proposals, which you are making to address the data requirement, should be accepted instead;
- a study required is not technically possible.

Other reasons may also be valid and it is up to you to decide on the appropriate basis for your case. Arguments should be supported by reference to appropriate data and a full list of the references cited should be provided. Any literature cited to support your case should be summarised in sufficient detail for the reader to determine the validity of the arguments presented. If you refer to any literature owned by another company and not in the public domain, you will be required to demonstrate that you are entitled to make use of such data (for example by the letter of access system).

Your reasoned case should not just present a description of data but should also explain how these data relate to the data requirements; you must interpret your own data and make your own case. The Advisory Committee on Pesticides (ACP) has made it clear that BPU should not do this for you. However, before you compile the case, you should seek our advice on the nature and extent of the data you intend to present, to ensure that you are clear on what information is required by the ACP.

Your case should stand alone as a document since it will be presented to the committee(s) in the format in which is submitted to BPU. BPU will draft an evaluation to accompany reasoned cases but we cannot incorporate the cases into our own papers. We will not, therefore, be improving on presentation or the arguments made.

The documents you provide should be in English and be typewritten. The quality of print should be sufficiently good that photocopies will be legible.

While it is the ACP that makes recommendations to Ministers as to whether to accept a reasoned case, BPU now has some experience of the standard of cases expected by the committees. Where necessary we will advise a company if we believe a reasoned case needs to be improved; however, we cannot guarantee that any case will be accepted by the ACP.

REFERENCES (relevant to the production of this guidance document)

The Control of Pesticides Regulations 1986. Statutory Instrument 1986/1510 is available from the Stationery Office. This was amended in 1997 by Statutory Instrument 1997/188 (which is also available from the Stationery Office).

Registration Handbook. This is a guide for applicants produced by The Health & Safety Executive's Biocides and Pesticides Assessment Unit and is provided free of charge to all approval holders.

CIPAC : MT46.3 Accelerated Storage Procedure. Collaborative International Pesticides Analytical Council Ltd, 2000 (Dobrat & Martin, Eds.) Published by Black Bear Press Ltd.

CIPAC : MT39.3 Storage of Liquids at 0°C - Collaborative International Pesticides Analytical Council Ltd, 1994 (Dobrat & Martin, Eds.) Published by Black Bear Press Ltd.

The Good Laboratory Practice Regulations 1999, Statutory Instrument 1999/3106 available from the Stationery Office

Validation Guidelines - Guidelines for validation of analytical methods for non-agricultural pesticide active ingredients and their respective products, produced by the Health & Safety Executives Biocides and Pesticides Assessment Unit.

Manual for the Development of FAO and WHO Specifications for Pesticides (First Edition)

GLOSSARY OF TERMS USED IN THIS DOCUMENT

ACP	The Advisory Committee on Pesticides is an impartial, appointed body of experts whose function is to advise Ministers on pesticide issues.
Active ingredient	The component of a product which fits it for use as a pesticide.
Approval	An approval given jointly by Ministers under Regulation 5 of The Control of Pesticides Regulations 1986 (as amended) (COPR).
ASTM	The American Society for Testing and Materials.
BPU	The Biocides and Pesticides Unit of HSE that deals with the registration of non-agricultural pesticides.
Batch	A defined quantity of material produced in a single series of operations.
CIPAC	Collaborative International Pesticides Analytical Council.
Committees	The Advisory Committee on Pesticides (ACP), established under SI 1985 No 1517, and the Interdepartmental Secretariat (IDS).
Evaluation	A written assessment of study reports or other data examined in the course of an appraisal by the Registration Authority.
FAO	The Food and Agriculture Organisation.
Formulation	A pesticide preparation containing technical active ingredient(s) and formulant(s) in a form suitable for use.
Non-Agricultural Pesticide	Non-agricultural pesticides are pesticides normally used in domestic situations or in aquaculture and include wood preservatives, surface biocides, antifouling products, rodenticides and insecticides/acaricides for use in public hygiene situations.

Pesticide

As defined in The Food and Environment Protection Act 1985 (FEPA) (Part III., section 16 (15) + (16)) and COPR (section 3, (1)).

Pesticides Newsletter

This is a quarterly newsletter on non-agricultural pesticides issues produced by BPU. Copies of the Newsletter can be downloaded from BPU's website (address given in the text).