REGISTRATION OF VETERINARY PESTICIDE PRODUCTS

GUIDELINES FOR SUBMISSION OF APPLICATIONS

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LIST OF ABBREVIATIONS

AA	Annual Average
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism And Excretion
AOEL	Acceptable Operator Exposure Levels
AP	Acidification Potential
API	Active Pharmaceutical Ingredients
ARFD	Acute Reference Dose
AUC	Area Under The Curve
BCOP	Bovine Corneal Opacity And Permeability
CA	Chemical Abstracts
CAS	Chemical Abstracts Service
CIPAC	Collaborative International Pesticides Analytical Council
COA	Certificate of Analysis
EC	European Commission
EC_X	Effective Concentration
EG	Emulsified Granules
EP	Eutrophication Potential
EQS	Environmental Quality Standards
FIFO	First In First Out
FISH	Fluorescence In-Situ Hybridisation
FPP	Finished Pharmaceutical Products
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
GWP	Global Warming Potential
HET-CAM	Hen's Egg Test - Chorio-Allantoic Membrane
HPLC	High-Performance Liquid Chromatography
HQ	Hazard Quotient
HR	Highest Residue
ICE	Isolated Chicken Eye
ILV	Independent Laboratory Validation
IR	Infrared
IRE	Isolated Rabbit Eye Test
ISO	International Organization For Standardization
IUPAC	International Union Of Pure And Applied Chemistry
JMPS	Joint Meeting on Pesticide Specifications

LD_{50}	The amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals
LLC	Lowest Lethal Concentration
LLNA	Local Lymph Node Assay
LOQ	Limit Of Quantification
MAC	Maximum Acceptable Concetration
MRL	Maximum Residue Levels
MS	Mass Spectra
NMR	Nuclear Magnetic Resonance
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
OECD	Organization for Economic Co-operation and Development
OD	Oil-based Suspension Concentrates
OPD	Ozone Depleting Potential
PEC	Predicted Environmental Concentration
PEC_A	Predicted environmental concentration in air
PEC_{GW}	Predicted environmental concentration in groundwater
PEC_S	Predicted environmental concentration in soil
PEC_{SED}	Predicted environmental concentration in sediment
PEC_{SW}	Predicted environmental concentration in surface water
POCP	Photochemical Ozone Creation Potential
POP	Persistent Organic Pollutant
PSUR	Periodic Safety Update Reports
QSPR	Quantitative Structure Property Relationship
RQ	Risk Quotient
STP	Sewage Treatment Plant
STMR	Supervised Trials Median Residue
SE	Suspo-Emulsions
TER	Toxic Exposure Ratio
TK	Technical Concentrate
UV/VIS	Ultraviolet/Visible
VPP	Veterinary Pesticide Product

INTRODUCTION

These guidelines present technical requirements for the preparation of an application that will be submitted to the Authority for registration of veterinary pesticides active substances and finished products.

These guidelines are arranged into parts A and B setting out the technical requirements for registration of active substances and finished products respectively. Arrangement of sections in the two parts are outlined in Tables 1.1 and 1.2.

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Scope

These guidelines provide guidance to the applicants on the arrangement of information to be provided to the Authority in seeking marketing authorization for pesticide products for veterinary use. It also assists the Authority during the evaluation and registration processes for such products.

Preparation and Presentation of Information

i. The applicant shall prepare and present the product dossier information according to the requirements as stipulated in these guidelines:
ii. The application should be typed in English. Any document that is in any language other than English must be accompanied by a certified or notarized English translation.
iii. The application must contain a complete index to the various appendices.
iv. All pages of the application should be numbered in the style: page x of y.
v. Payment of fees shall be made in accordance to Fifth Schedule of the regulations (LN. No. 209 of 2015)
vi. The application should be submitted in hard and soft copies (CD-ROM or External Driver) addressed to the authority
vii. The PDF documents should be in Optical Character Recognition, selectable and searchable
viii. A separate application is required for each product.

Officially Recognized References

- The official recognized pharmacopoeias by the Authority are British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.), The International Pharmacopoeia (Ph.Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP). References should be cited in accordance with the current edition of compendia.
- When reference is made to specifications, quality control procedures and test methods in official recognized compendia or scientific publications, **full** references and copies of relevant pages shall be enclosed.
- All in-house processes quoted in the documentation must be validated and appropriate references cited.

2 SUBMISSION OF APPLICATION

An application for product registration for either locally manufactured or imported products shall be made in writing via a cover letter and application form dated and signed by the applicant. If the applicant is a foreign company, the applicant shall appoint a local technical representative through whom an application shall be submitted. The local agent shall be a registered wholesale dealer.

The application should be submitted to Authority through the authorized local technical Representative to the following address:

The Chief Executive Officer
Veterinary Medicines Directorate
P. O. Box 66171-00800,
NAIROBI, KENYA
Email: vmd@kilimo.go.ke

Types of applications

For the purposes of submission to the Authority, applications are classified into four categories as follows:

2.1.1. **New applications for registration**

This is an application for registration of a veterinary pesticide product that is intended to be placed on the Kenyan market for the first time.

- The applicant may only make a new application and he/she shall be the person who signs the declaration part of the application form.
- A new application for veterinary pharmaceutical product registration in Kenya shall include the following:
    1. Signed and dated original hard-copy of cover letter
    2. Signed and dated application form for product registration
    3. Proof of payment of registration fee at the time of submission
    4. Hard copy of the Dossier
    5. Electronic copy (CD of memory stick) of the Dossier in PDF, QOS, QIS, in MS Word
    6. Three commercial samples of the veterinary pharmaceutical products with CoA.

2.1.2 Applications for Renewal of Registration

An application for renewal of a veterinary pesticide products shall be made to the Authority at least ninety (90) calendar days before expiration of the last registration by completion of the prescribed application form.

If an application for renewal is not made within three (3) months of grace period following the expiration of the registration validity, it shall be considered as a new application for registration.

Applications for renewal of registration shall be made by submission of the following:

1. Dully filled application form for renewal of registration.
2. Long term stability report for three commercial batches of the finished product
3. Periodic Safety Update Reports (PSUR)
4. Two commercial samples of the VPP with CoAs
5. A non-refundable application fee for renewal of registration
6. Any other requirements that the Authority may determine from time to time as informed by pharmacovigilance reports.

2.1.3 Application for Variation of a registered veterinary pesticide product

Any variation to a registered VPP information shall be notified in writing to the Authority through an application in the approved format.

An application for variation shall be submitted as per the requirements set out in the Guidelines for Variation of Registered Veterinary Pesticide Products in force at the time of submission.

2.1.4. Retention of a veterinary pesticide product on the register

Every marketing authorization holder shall retain registered products in the register every year. This shall be done by completing the application form for retention of a veterinary medicine and pay annual retention fees as stipulated in the regulations (LN. No. 209 of 2015). Applications for retention of a registered product for a particular year shall be made by 31st of December of the preceding year. Application received beyond this date will be penalized.

Receiving of new applications

An application consists of electronic copies, online submission or specified hard copies where applicable. The Authority only receives the application of product registration when the payment of prescribed registration fees is made. After receiving a product registration application, a reference number is assigned to the application and it will be used in all subsequent correspondences relating to the application.

Evaluation Procedures

1. After receiving the VPP registration application, the Authority shall proceed with screening of the dossier for completeness. In the event that the dossier is incomplete, it will not be scheduled for assessment and the applicant will be notified within 30 working days and requested to comply with requirements in writing.
2. In case of a positive outcome during the screening, the application will be subjected for assessment according to the First in First out (FIFO) basis.
3. Priority assessment may be granted for applications for renewal of registration.
4. Two assessors to provide scientific and regulatory oversight regarding the quality, safety and efficacy of the product under assessment review a product dossier.
5. The Authority reserves the right to request any additional information to the applicant for establishing the quality, safety and efficacy of veterinary pharmaceutical products in Kenya. During the assessment, additional data and/or samples may be requested through an official communication letter.
    a) Once a query has been issued to the applicant, the assessment process stops until the Authority receives a written response to the raised queries.

b) Further processing of the application may only be undertaken if responses to queries issued in the official communication letter contains all outstanding information requested in one submission.

c) Failure to comply with this condition or if the queries have been reissued for a second time and the applicant provides unsatisfactory responses, the application will be rejected.

d) In the event that the responses to the queries are not submitted within ninety (90) calendar days from the date they were issued, it will be considered that the applicant has withdrawn the application unless the applicant has requested for extension of deadline.

e) In cases of rejected applications, registration may only be considered upon submission of a new application 12 months from the date of rejection.

Compliance to the current Good Manufacturing Practices (cGMP)

The GMP inspection is part of the VPP registration process.

1. The Authority will conduct inspection of the facility or use other means to verify whether the manufacturing site complies with cGMP requirements and/or guidelines before a product is registered.
2. No product shall be registered unless the facility complies with cGMP. During the assessment, assessors may highlight GMPs issues and communicate to the department that has mandate of inspection and compliance.

Field Efficacy Trials

Local field experimental studies are required before registration of a veterinary pesticide product intended. These studies shall be carried out in laboratories designated by the Authority. The applicant will bear all the related costs.

Technical and Registration Committee of the Council

1. After dossier evaluation is done, a final dossier assessment report shall be presented to technical and registration committee before final decision is made by the Council for granting or rejecting registration of the product.
2. In the event, that there is safety, quality or efficacy issues to be resolved as per the decision of the technical committee, the application shall remain pending until the resolution of the raised issues.
3. If the applicant fails to provide the required data within ninety calendar days (90), it will be considered that applicant has withdrawn the application.
4. In cases of rejected applications, registration may only be considered upon submission of a new application 12 months from the date of rejection.

The Authority will register a product in the event that data on safety, quality and efficacy is considered satisfactory and a registration certificate will be granted. The registration shall be valid for a period of five

(5) years. In the event the Authority suspends or cancels the registration validity, a written official communication shall be made to the applicant.

Timelines for Registration

1. Product dossiers shall be scheduled for assessment according to the First in First out (FIFO) basis upon compliance of the requirements. A new application shall be processed within eighteen (18) months of receipt of the application.
2. Post Approval Variation and Renewal of registration; Complete applications will be processed within six (6) months of receiving the application including evaluation of documentation and consideration by a committee on product registration.
3. The applicant will be required to provide any requested additional data within ninety (90) calendar days. Additional data or query responses shall be processed within sixty (60) calendar days.

PART A: REGISTRATION OF ACTIVE SUBSTANCE

TECHNICAL INFORMATION REQUIRED

INTRODUCTION

The information submitted shall meet the following requirements;

1.1 The information shall be sufficient to evaluate the foreseeable risks, whether immediate or delayed, which the active substance may entail for humans, including vulnerable groups, animals and the environment and contain at least the information and results of the studies referred to in this guidelines.

1.2 Any information on potentially harmful effects of the active substance, its metabolites and impurities on human and animal health or on groundwater shall be included.

1.3 Any information on potentially unacceptable effects of the active substance, its metabolites and impurities on the environment, on plants and plant products shall be included.

1.4 The information shall include all relevant data from the scientific peer reviewed open literature on the active substance, metabolites and breakdown or reaction products and finished products containing the active substance and dealing with side-effects on health, the environment and non-target species. A summary of this data shall be provided.

1.5 The information shall include a full and unbiased report of the studies conducted as well as a full description of them. Such information shall not be required, where one of the following conditions is fulfilled:

a) It is not necessary owing to the nature of the product or its proposed uses, or it is not scientifically necessary;
b) It is technically not possible to supply.

In such a case a justification shall be provided.

1.6 The simultaneous use of the active substance as a biocide shall be reported.

1.7 Where relevant, the information shall be generated using test methods which are referred to in these guidelines.

1.8 The information shall include a full description of the test methods used.

1.9 The information shall include a list of endpoints for the active substance.

1.10 The information on the active substance, taken together with the information concerning one or more finished products containing the active substance and together, if appropriate, with the information concerning safeners and synergists and other components of the finished products, shall be sufficient to:

a) Permit an assessment of the risks for humans, associated with handling and use of finished products containing the active substance;
b) permit an assessment of the risks for human and animal health, arising from residues of the active substance and its metabolites, impurities, breakdown and reaction products remaining in water, air, food and feed;

c) Predict the distribution, fate and behaviour in the environment of the active substance and metabolites, breakdown and reaction products, where they are of toxicological or environmental significance, as well as the time courses involved;
d) Permit an assessment of the impact on non-target species (flora and fauna), including the impact on their behaviour, which are likely to be exposed to the active substance, its metabolites, breakdown

and reaction products, where they are of toxicological or environmental significance. Impact can result from single, prolonged or repeated exposure and can be direct or indirect, reversible or irreversible;

e) Evaluate the impact on biodiversity and the ecosystem;
f) Identify non-target species and populations for which hazards arise because of potential exposure;
g) Permit an evaluation of short and long-term risks for non-target species, populations, communities and processes;
h) Classify the active substance as to hazard
i) Specify the pictograms, the signal words, and relevant hazard and precautionary statements for the protection of man, non-target species and the environment, which are to be used for labelling purposes;
j) Establish, where relevant, an acceptable daily intake (ADI) level for humans;
k) Establish acceptable operator exposure levels (AOEL);
l) Establish, where relevant, an acute reference dose, (ARfD) for humans;
m) Identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of poisoning in humans;
n) Establish the isomeric composition and the possible metabolic conversion of the isomers, when relevant;
o) Establish residues definitions appropriate for risk assessment;
p) Establish residues definitions appropriate for monitoring and enforcement purposes;
q) Permit a risk assessment of consumer exposure, including, where relevant, a cumulative risk assessment deriving from exposure to more than one active substance;
r) permit an estimation of the exposure to operators, workers, residents and bystanders including, where relevant, the cumulative exposure to more than one active substance;
s) Establish maximum residue levels and concentration/dilution factors
t) Permit an evaluation to be made as to the nature and extent of the risks for man, animals (species normally fed and kept by humans or food producing animals) and of the risks for other non-target vertebrate species;
u) Identify measures necessary to minimise contamination of the environment and impact on non-target species;
v) Decide whether or not the active substance has to be considered as persistent organic pollutant (POP), persistent, bio accumulative and toxic (PBT) or very persistent and very bio accumulative (vPvB)
w) Decide whether or not the active substance has to be considered as a candidate for substitution
x) Decide whether or not the active substance has to be considered as a low-risk active substance
y) Decide whether, or not, the active substance is to be approved;
z) Specify conditions or restrictions to be associated with any approval.

1.11 Where relevant, tests shall be designed and data analysed using appropriate statistical methods.

1.12 Exposure calculations shall refer to scientific methods accepted by VMD, when available. Additional methods, when used, shall be justified.

1.13 For each section of the data requirements, a summary of all data, information and evaluation made shall be submitted.

2. The requirements set out in this guidelines shall represent the minimum data to be submitted. Additional requirements may be necessary in specific circumstances, that is to say specific scenarios, patterns of use other than those taken into account for approval. Careful attention shall be given to environmental, climatic and agronomic conditions when tests are set up and approved by the competent authorities.

3. Good laboratory practice (GLP)

3.1 Where testing is done to obtain data on the properties or safety with respect to human or animal health or the environment, these will be done in accordance with GLP

3.2 For analytical test, if shall be done in accordance with the GLP requirements and shall be conducted by laboratories accredited for the relevant method.

4. Test material

4.1 A detailed description (specification) of the material used shall be provided. Where tests are done using the active substance, the material used shall comply with the specification that will be used in the manufacture of the finished product to be authorised, except where radio-labelled material or the purified active substance is used.

4.2 Where studies are conducted using an active substance produced in the laboratory or in a pilot plant production system, the studies shall be repeated using the active substance as manufactured, unless the applicant shows that the test material used is essentially the same, for the purposes of toxicological, ecotoxicological, environmental and residue testing and assessment. In cases of uncertainty, bridging studies shall be submitted to serve as a basis for a decision as to the possible need for repetition of the studies.

4.3 Where studies are conducted using an active substance of different purity or which contains different impurities or different levels of impurities to the technical specification or where the active substance is a mixture of components, the significance of the differences shall be addressed either by data or scientific case. In cases of uncertainty, appropriate studies using the active substance as manufactured for commercial production shall be submitted to serve as a basis for a decision.

4.4 In the case of studies in which dosing extends over a period (for example repeated dose studies), dosing shall be done using a single batch of active substance if stability permits. Whenever a study implies the use of different doses, the relationship between dose and adverse effect shall be reported.

4.5 When tests shall be conducted using purified active substance (≥ 980 g/kg) of stated specification, the purity of such test material shall be as high as can be achieved using the best available technology and shall be reported. A justification shall be provided in cases where the degree of purity achieved is less than 980 g/kg. Such justification shall demonstrate that all technically feasible and reasonable possibilities for the production of the purified active substance have been exhausted.

4.6 Where radio-labelled test material is used, radio-labels shall be positioned at sites (one or more as necessary), to facilitate elucidation of metabolic and transformation pathways and to facilitate investigation of the distribution of the active substance and of its metabolites, reaction and breakdown products.

5. Tests on vertebrate animals

5.1 Where tests on vertebrate animals are undertaken, reduction and refinement methods for *in vivo* testing shall be encouraged to keep the number of animals used in testing to a minimum.

5.2 The principles of replacement, reduction and refinement of the use of animals shall be taken into account in the design of the test methods, in particular when appropriate validated methods become available to replace, reduce or refine animal testing.

5.3 Tests involving the deliberate administration of the active substance or the finished products to humans and non-human primates shall not be performed for the purpose of this guideline.

5.4 For ethical reasons, study designs shall be carefully considered, taking into account the scope for reduction, refinement and replacement of animal tests. For example, by including one or more additional dose groups or time points for blood sampling in one study, it may be possible to avoid the need for another study.

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PART A: SECTION 1

IDENTITY OF THE ACTIVE SUBSTANCE

The information provided shall be sufficient to precisely identify each active substance and define it in terms of its specification and nature.

1.1. Applicant

The name and address of the applicant shall be provided, as well as the name, position, telephone, e-mail address and telefax number of a contact point.

1.2. Manufacturer/Producer

The name and address of the producer of the active substance shall be provided, as well as the name and address of each manufacturing plant in which the active substance is manufactured. A contact point (name, telephone, e-mail address and telefax number) shall be provided.

1.3. Common name proposed or ISO-accepted, and synonyms

The International Organization for Standardization (ISO) common name, or proposed ISO common name and where relevant, other proposed or accepted common names (synonyms), including the name (title) of the nomenclature authority concerned, shall be provided.

1.4. Chemical name (IUPAC and CA nomenclature)

The chemical name as given in accordance with both the International Union of Pure and Applied Chemistry (IUPAC) and Chemical Abstracts (CA) nomenclature, shall be provided, where applicable.

1.5. Producer's development code numbers

Code numbers used to identify the active substance, and where available, formulations containing the active substance, during development work, shall be reported. For each code number reported, the material to which it relates, the period for which it was used, and the Member States or other countries in which it was used and is being used, shall be stated.

1.6. CAS, EC and CIPAC numbers

Chemical Abstracts Service (CAS), European Commission (EC) and Collaborative International Pesticides Analytical Council (CIPAC) numbers, where they exist, shall be reported.

1.7. Molecular and structural formula, molar mass

The molecular formula, molar mass and structural formula of the active substance, and where relevant, the structural formula of each isomer present in the active substance, shall be provided.

For plant extracts, a different approach may be taken if adequately justified.

1.8. Method of manufacture (synthesis pathway) of the active substance

The method of manufacture, in terms of the identity (name, CAS number, structural formula) and purity of the starting materials and whether they are commercially available, the chemical pathways involved, and the identity of impurities present in the final product, shall be provided, for each manufacturing plant. Detailed information shall be given as to the origin of those impurities. Each impurity shall be categorised as resulting from side reactions, impurities in the starting material, remaining reaction intermediates or starting materials. Their toxicological, ecotoxicological and environmental relevance shall be addressed. This information shall also include impurities that are not detected but that could theoretically be formed. Generally process engineering information is not required.

1.9. Specification of purity of the active substance in g/kg

The minimum content in g/kg of pure active substance in the manufactured material used for production of finished product, shall be reported. A justification shall be provided for the minimum content proposed in the specification; this shall include

a statistical analysis of the data on at least five representative batches, as referred to in point 1.11. Additional supporting data may be provided to further justify the technical specification.

If the active substance is manufactured as technical concentrate (TK), the minimum and maximum content of the pure active substance shall be given, along with its content in the theoretical dry weight material.

If the active substance is a mixture of isomers, the ratio or the ratio range of the content of isomers shall be provided. The relative biological activity of each isomer, both in terms of efficacy and toxicity, shall be reported.

For plant extracts, a different approach may be taken if adequately justified.

1.10. Identity and content of additives (such as stabilisers) and impurities

The minimum and maximum content in g/kg of each additive shall be provided.

The maximum content in g/kg of each further component other than additives shall also be provided.

If the active substance is manufactured as technical concentrate (TK), the maximum content of each impurity shall be given, along with their content in the theoretical dry weight material.

Isomers that are not part of the ISO common name are considered as impurities.

Where the information provided does not fully identify a component (for example condensates), detailed information on the composition shall be provided for each such component.

For plant extracts, a different approach may be taken if adequately justified.

1.10.1. Additives

The trade name of components added to the active substance, prior to manufacture of the finished, to preserve stability and facilitate ease of handling, hereinafter 'additives', shall also be provided. The following information shall, where relevant, be provided for such additives:

(a) chemical name in accordance with IUPAC and CA nomenclature;

(b) ISO common name or proposed common name if available;

(c) CAS number, EC number;

(d) molecular and structural formula;

(e) molar mass;

(f) minimum and maximum content in g/kg; and

(g) function (for example stabiliser).

1.10.2. Significant impurities

Impurities present in quantities of 1 g/kg or more shall be considered as significant. For significant impurities the following information, where relevant, shall be provided:

(a) chemical name in accordance with IUPAC and CA nomenclature;

(b) ISO common name or proposed common name, if available;

(c) CAS number, EC number;

(d) molecular and structural formula;

(e) molar mass; and

(f) maximum content in g/kg.

Information on how the structural identity of the impurities was determined shall be given.

1.10.3. Relevant impurities

Impurities that are particularly undesirable because of their toxicological, ecotoxicological or environmental properties, shall be considered as relevant. For relevant impurities the following information, where relevant, shall be provided:

(a) chemical name in accordance with IUPAC and CA nomenclature;

(b) ISO common name or proposed common name if available;

(c) CAS number, EC number;

(d) molecular and structural formula;

(e) molar mass; and

(f) maximum content in g/kg.

Information on how the structural identity of the impurities was determined shall be reported.

1.11. Analytical profile of batches

At least five representative batches from recent and current industrial scale production of the active substance shall be analysed for content of pure active substance, impurities, additives and each further component other than additives, as appropriate. All of the representative batches shall be within the last five years of manufacture. Where data from the last five years of production are not available, a justification shall be provided. The analytical results reported shall include quantitative data, in terms of g/kg content, for all components present in quantities of 1 g/kg or more and typically should account for at least 980 g/kg of the material analysed. The statistical basis for the content proposed in the technical specification shall be explained (for example: maximum level found in practice, average plus three standard deviations of levels found in practice, etc.). Supporting data may be provided to further justify the technical specification. The actual content of components which are particularly undesirable because of their toxicological, ecotoxicological or environmental properties shall be determined and reported even if present in quantities below 1 g/kg. Data reported shall include the results of the analysis of individual samples and a summary of that data, to show the minimum, maximum and mean content of each relevant component.

Where an active substance is produced in different manufacturing plants the information set out in the first paragraph shall be provided for each of the plants separately.

In addition, where relevant, samples of the active substance produced at laboratory scale or in pilot production systems, shall be analysed, if such material was used in generating toxicological or ecotoxicological data. If this data is not available a justification shall be provided.
Where the information provided relates to a pilot plant production system, the information required shall again be provided once industrial scale production methods and procedures have stabilised. Where available, industrial scale data shall be provided before approval. Where data on industrial scale production are not available, a justification shall be provided.

PART A: SECTION 2

PHYSICAL AND CHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE

2.1. Melting point and boiling point

The melting point or where appropriate the freezing or solidification point of purified active substance shall be determined and reported. Measurements shall be taken up to 360 °C.

The boiling point of purified active substance shall be determined and reported. Measurements shall be taken up to 360 °C.

Where melting point or boiling point cannot be determined because of decomposition or sublimation, the temperature at which decomposition or sublimation occurs shall be reported.

2.2. Vapour pressure, volatility

The vapour pressure of purified active substance at 20 °C or 25 °C shall be reported. Where vapour pressure is less than 10^{-5} Pa at 20 °C the vapour pressure at 20 °C or 25 °C shall be estimated by a vapour pressure curve with measurements at higher temperatures.

In the case of active substances which are solids or liquids, volatility (Henry's law constant) of purified active substance shall be determined or calculated from its water solubility and vapour pressure and be reported (in $Pa \times m^3 \times mol^{-1}$).

2.3. Appearance (physical state, colour)

A description of both the colour, if any, and the physical state of both the active substance as manufactured and purified active substance, shall be provided.

2.4. Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity

The following spectra, including a table of signal characteristics needed for interpretation, shall be determined and reported: ultraviolet/visible (UV/VIS), infrared (IR), nuclear magnetic resonance (NMR) and mass spectra (MS) of purified active substance.

Molar extinction at relevant wavelengths shall be determined and reported (ε in $L \times mol^{-1} \times cm^{-1}$). Relevant wavelengths include all maxima in the UV/visible absorption spectrum, as well as the wavelength range of 290- 700 nm.

In the case of active substances which are resolved optical isomers, the optical purity shall be measured and reported.

Where necessary for the identification of the impurities considered to be of toxicological, ecotoxicological or environmental significance, the UV/visible absorption spectra, IR, NMR and MS spectra, shall be determined and reported.

2.5. Solubility in water

The water solubility of purified active substances under atmospheric pressure shall be determined and a value reported for 20 °C. These water solubility determinations shall be made in the neutral range (that is to say in distilled water in equilibrium with atmospheric carbon dioxide). If the pKa is between 2 and 12, water solubility shall also be determined in the acidic range (pH 4 to 5) and in the alkaline range (pH 9 to 10). Where the stability of the active substance in aqueous media is such that water solubility cannot be determined, a justification based on test data shall be provided.

2.6. Solubility in organic solvents

The solubility of the active substances as manufactured or purified active substance in the following organic solvents at 15 to 25 °C shall be determined and reported if less than 250 g/L; the temperature applied shall be specified. Results shall be reported as g/L.

(a) Aliphatic hydrocarbon: preferably heptane
(b) Aromatic hydrocarbon: preferably toluene

(c) Halogenated hydrocarbon: preferably dichloromethane

(d) Alcohol: preferably methanol or isopropyl alcohol

(e) Ketone: preferably acetone

(f) Ester: preferably ethyl acetate.

If for a particular active substance, one or more of those solvents is unsuitable (for example reacts with test material), alternative solvents may be used instead. In such cases, choices of solvents shall be justified in terms of their structure and polarity.

2.7. Partition coefficient n-octanol/water

The n-octanol/water partition coefficient (Kow or log Pow) of purified active substance and of all components of the residue definition for risk assessment shall be determined and reported for 20 °C or 25 °C. The effect of pH (4to 10) shall be investigated when the active substance has a pKa value between 2 and 12.

2.8 Dissociation in water

Where dissociation in water occurs, the dissociation constants (pKa values) of the purified active substance shall be determined and reported for 20 °C. The identity of the dissociated species formed, based on theoretical consider- ations, shall be reported. If the active substance is a salt the pKa value of the non-dissociated form of the active substance shall be given.

2.9. Flammability and self-heating

The flammability and self-heating of active substances as manufactured shall be determined and reported. A theoretical estimation based on structure shall be accepted if it meets the criteria set out in Appendix 6 of the United Nations' Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria (1). In justified cases, data for purified active substance may be used.

2.10. Flash point

The flash point of active substances as manufactured with a melting point below 40 °C shall be determined and reported. In justified cases, data for purified active substance may be used.

2.11. Explosive properties

The explosive properties of active substances as manufactured shall be determined and reported. A theoretical estimation based on structure shall be accepted if it meets the criteria set out in Appendix 6 of the United Nations 'Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria'. In justified cases, data for purified active substance may be used.

2.12. Surface tension

The surface tension of purified active substance shall be determined and reported.

2.13. Oxidising properties

The oxidising properties of active substances as manufactured, shall be determined and reported. A theoretical estimation based on structure shall be accepted if it meets the criteria set out in Appendix 6 of the United Nations 'Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria'. In justified cases data for purified active substance may be used.

2.14. Other studies

Supplementary studies necessary for the classification of the active substance by hazard shall be carried out

PART A: SECTION 3

FURTHER INFORMATION ON THE ACTIVE SUBSTANCE

3.1. Use of the active substance

The information provided shall describe the intended purposes for which finished product containing the active substance are used, or are to be used and the dose and manner of their use or proposed use.

3.2. Function

The function shall be specified from among the following:

(a) acaricide;

(b) other (shall be specified by the applicant).

3.3. Effects on Pests

The nature of the effects on harmful organisms shall be stated:

(a) contact action;

(b) stomach action;

(c) inhalation action;

(d) fungitoxic action;

(e) fungistatic action;

(f) desiccant;

(g) reproduction inhibitor;

(h) other (shall be specified by the applicant).

3.4. Harmful organisms controlled

Details of existing use and the intended use in terms of animals treated and where relevant protected shall be provided.

Where relevant, details of harmful organisms against which protection is afforded shall be provided.

Where relevant, effects achieved, shall be reported.

3.5 Mode of action

To the extent that it has been elucidated, a statement shall be provided as to the mode of action of the active substance in terms, where relevant, of the biochemical and physiological mechanisms and biochemical pathways involved. Where available, the results of relevant experimental studies shall be reported.

Where it is known that to exert its intended effect, the active substance has to be converted to a metabolite or breakdown product following application or use of finished product containing it, the following information shall be provided for active metabolite or breakdown products:

(a) chemical name in accordance with IUPAC and CA nomenclature;

(b) ISO common name or proposed common name;

(c) CAS-number EC number;

(d) molecular and structural formula; and

(e) molar mass.

The information referred to in points (a) to (e) shall be cross referenced to and drawing on information provided under Sections 5 to 8, where relevant.

Available information relating to the formation of active metabolites and breakdown products shall be provided. Such information shall include:
— the processes, mechanisms and reactions involved,
— kinetic and other data concerning the rate of conversion and if known the rate limiting step,
— environmental and other factors effecting the rate and extent of conversion.

3.5. Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies

Where available, information on the occurrence or possible occurrence of the development of resistance or cross- resistance shall be provided.

Appropriate risk management strategies shall be addressed for national/regional areas.

3.6. Methods and precautions concerning handling, storage, transport or fire

A safety data sheet shall be provided for all active substances.

The studies, data and information submitted, together with other relevant studies, data and information, shall both specify and justify the methods and precautions to be followed in the event of fire. The possible products of combustion in the event of fire shall be estimated, based on the chemical structure and the chemical and physical properties of the active substance.

3.7. Procedures for destruction or decontamination

In many cases the preferred or sole means to safely dispose of active substances, contaminated materials, or contaminated packaging is through controlled incineration in a licensed incinerator.

Other methods to dispose of the active substance, contaminated packaging and contaminated materials, where proposed, shall be fully described. Data shall be provided for such methods, to establish their effectiveness and safety.

3.8. Emergency measures in case of an accident

Procedures for the decontamination of water and soil in case of an accident shall be provided.

The studies, data and information submitted, together with other relevant studies, data and information, shall demonstrate the suitability of measures proposed for use in emergency situations.

PARTA: SECTION 4

ANALYTICAL METHODS

Introduction

The provisions of this Section cover analytical methods used for the generation of pre-approval data and required for post-approval control and monitoring purposes.

Descriptions of methods shall be provided and include details of equipment, materials and conditions used. On request, the following shall be provided:

(a) analytical standards of the purified active substance;
(b) samples of the active substance as manufactured;
(c) analytical standards of relevant metabolites and all other components included in all monitoring residue definitions;
(d) samples of reference substances for the relevant impurities.

Where possible, the standards referred to in points (a) and (c) shall be made commercially available and, on request, the distributing company shall be named.

4.1. Methods used for the generation of pre-approval data

4.1.1. Methods for the analysis of the active substance as manufactured

Methods shall be provided, with a full description, for the determination of:

(a) pure active substance in the active substance as manufactured and specified in the dossier submitted in support of approval
(b) significant and relevant impurities and additives (such as stabilisers) in the active substance as manufactured.

The applicability of existing CIPAC methods shall be assessed and reported. In case of use of a CIPAC method, further validation data shall not be required, but example chromatograms shall be submitted, where available.

The specificity of the methods shall be determined and reported. In addition, the extent of interference by other substances present in the active substance as manufactured (such as impurities or additives), shall be determined.

The linearity of methods shall be determined and reported. The calibration range shall extend (by at least 20 %) beyond the highest and lowest nominal content of the analyte in relevant analytical solutions. Either duplicate determinations at three or more concentrations or single determinations at five or more concentrations shall be made. The equation of the calibration line and the correlation coefficient shall be reported and a typical calibration plot shall be submitted. In cases where a non-linear response is used, this shall be justified by the applicant.

The precision (repeatability) of the methods shall be determined and reported. A minimum of five replicate sample determinations shall be made and the mean, the relative standard deviation and the number of determinations shall be reported.

For the determination of the active substance content, an assessment of accuracy of the method shall be made by an assessment of the interference and precision.

As regards additives and significant and relevant impurities:

— the accuracy of the methods shall be determined on at least two representative samples at levels appropriate to the batch data and material specification. The mean and the relative standard deviation of the recoveries shall be reported,

— the experimental determination of the limit of quantification (LOQ) shall not be required. However, it shall be demonstrated that the methods are sufficiently precise to analyse significant impurities at levels appropriate to the material specification and relevant impurities at a concentration equivalent to at least 20 % less than the specification limit.

4.1.2. Methods for risk assessment

Methods shall be submitted, with a full description, for the determination of non-isotope-labelled residues in all areas of the dossier, as set out in detail in the following points:

(a) in soil, water, sediment, air and any additional matrices used in support of environmental fate studies;

(b) in soil, water and any additional matrices used in support of efficacy studies;

(c) in feed, body fluids and tissues, air and any additional matrices used in support of toxicology studies;

(d) in body fluids, air and any additional matrices used in support of operator, worker, resident and bystander exposure studies;

(e) in soil, water, sediment, feed and any additional matrices used in support of ecotoxicology studies;

(f) in water, buffer solutions, organic solvents and any additional matrices used in the physical and chemical properties tests.

The specificity of the methods shall be determined and reported. Validated confirmatory methods shall be submitted if appropriate.

The linearity, recovery and precision (repeatability) of methods shall be determined and reported.

Data shall be generated at the LOQ and either the likely residue levels or ten times the LOQ. Where relevant, the LOQ shall be determined and reported for each analyte.

4.2. Methods for post-approval control and monitoring purposes

Methods, with a full description, shall be submitted for:

(a) the determination of all components included in the monitoring residue definition as submitted in accordance with the provisions of point 6.7.1 in order to determine compliance with established maximum residue levels (MRLs); they shall cover residues in or on food and feed of plant and animal origin;

(b) the determination of all components included for monitoring purposes in the residue definitions for soil and water as submitted in accordance with the provisions of point 7.4.2;

(c) the analysis in air of the active substance and relevant breakdown products formed during or after application, unless the applicant shows that exposure of operators, workers, residents or bystanders is negligible;

(d) the analysis in body fluids and tissues for active substances and relevant metabolites.

As far as practicable these methods shall employ the simplest approach, involve the minimum cost, and require commonly available equipment.

The specificity of the methods shall be determined and reported. It shall enable all components included in the monitoring residue definition to be determined. Validated confirmatory methods shall be submitted if appropriate.

The linearity, recovery and precision (repeatability) of methods shall be determined and reported.

Data shall be generated at the LOQ and either the likely residue levels or ten times the LOQ. The LOQ shall be determined and reported for each component included in the monitoring residue definition.

For residues in or on food and feed of plant and animal origin and residues in drinking water, the reproducibility of the method shall be determined by means of an independent laboratory validation (ILV) and reported.

PART A: SECTION 5

TOXICOLOGICAL AND METABOLISM STUDIES

Introduction

1. The relevance of generating toxicity data in animal models with dissimilar metabolic profiles to those found in humans shall be addressed, if such metabolic information is available, and taken into consideration for study design and risk assessment.

2. All potentially adverse effects found during toxicological investigations (including effects on organs/systems such as the immune system, the nervous system, or the endocrine system) shall be reported. Additional studies may be necessary to investigate the mechanisms underlying effects that could be critical to hazard identification or risk assessment.

   All available biological data and information relevant to the assessment of the toxicological profile of the active substance tested, including modelling, shall be reported.

3. Where available, historical control data shall be provided routinely. The data submitted shall be for endpoints that could represent critical adverse effects, and shall be strain-specific and from the laboratory which carried out the index study. They shall cover a five-year period, centred as closely as possible on the date of the index study.

4. When preparing a study plan, available data on the test substance, such as its physico-chemical properties (such as volatility), purity, reactivity (such as rate of hydrolysis, electrophilicity) and structure-activity relationships of chemical analogues, shall be taken into account.

5. For all studies actual achieved dose in mg/kg body weight, as well as in other convenient units (such as mg/L inhalation, mg/cm^2 dermal), shall be reported.

6. The analytical methods to be used in toxicity studies shall be specific for the entity to be measured and shall be adequately validated. The LOQ shall be adequate for the measurement of the range of concentration anticipated to occur in the generation of the toxicokinetic data.

7. Where, as a result of metabolism or other processes in or on treated plants, in livestock, in soil, in ground water, open air, or as a result of processing of treated products, the terminal residue to which humans will be exposed contains a substance which is not the active substance itself and is not identified as a significant metabolite in mammals, toxicity studies shall, where technically possible, be carried out on that substance unless it can be demonstrated that human exposure to that substance does not constitute a relevant risk to health.

   Toxicokinetic and metabolism studies relating to metabolites and breakdown products shall only be required if toxicity findings of the metabolite cannot be evaluated by the available results relating to the active substance.

8. The oral route shall always be used if it is practical. In cases where exposure of humans is mainly by the gas phase, it can be more appropriate to perform some of the studies via inhalation.

9. For dose selection, toxicokinetic data such as saturation of absorption measured by systemic availability of substance and/or metabolites shall be taken into consideration.

5.1. Studies on absorption, distribution, metabolism and excretion in mammals

Information on blood and tissues concentration of the active substance and relevant metabolites, for example around the time to reach the maximum plasma concentration (T_{max}), shall be generated in short and long-term studies on relevant species to enhance the value of the toxicological data generated in terms of understanding the toxicity studies.

The main objective of the toxicokinetic data is to describe the systemic exposure achieved in animals and its relationship to the dose levels and the time course of the toxicity studies.

Other objectives are:

(a) to relate the achieved exposure in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to human health, with a particular regard to vulnerable groups;

b) to support the design of a toxicity study (choice of species, treatment regimen, selection of dose levels) with respect to kinetics and metabolism;

(b) to provide information which, in relation to the findings of toxicity studies, contributes to the design of supplementary toxicity studies as outlined in point 5.8.2;

(c) to compare the metabolism of rats with the metabolism in livestock as outlined in point 6.2.4.

5.1.1. Absorption, distribution, metabolism and excretion after exposure by oral route

Limited data restricted to one *in vivo* test species (normally rat) may be all that is required as regards absorption, distribution, metabolism and excretion after exposure by oral route. These data can provide information useful in the design and interpretation of subsequent toxicity tests. However, it shall be remembered that information on interspecies differences is crucial in extrapolation of animal data to humans and information on metabolism following administration via other routes may be useful in human risk assessments.

It is not possible to specify detailed data requirements in all areas, since the exact requirements will depend upon the results obtained for each particular test substance.

The studies shall provide sufficient information about the kinetics of the active substance and its metabolites in relevant species after being exposed to the following:

(a) a single oral dose (low and high dose levels);
(b) an intravenous dose preferably or, if available, a single oral dose with assessment of biliary excretion (low dose level); and
(c) a repeated dose.

A key parameter is systemic bioavailability (F), obtained by comparison of the area under the curve (AUC) after oral and intravenous dosing.
When intravenous dosing is not feasible a justification shall be provided. The design of the

kinetic studies required shall include:

(a) an evaluation of the rate and extent of oral absorption including maximum plasma concentration (C_{max}), AUC, T_{max} and other appropriate parameters, such as bioavailability;

(b) the potential for bioaccumulation;
(c) plasma half-lives;
(d) the distribution in major organs and tissues;
(e) information on the distribution in blood cells;
(f) the chemical structure and the quantification of metabolites in biological fluids and tissues;
(g) the different metabolic pathways;
(h) the route and time course of excretion of active substance and metabolites;

(i) investigations whether and to what extent enterohepatic circulation takes place.

Comparative *in vitro* metabolism studies shall be performed on animal species to be used in pivotal studies and on human material (microsomes or intact cell systems) in order to determine the relevance of the toxicological animal data and to guide in the interpretation of findings and in further definition of the testing strategy.

An explanation shall be given or further tests shall be carried out where a metabolite is detected *in vitro* in human material and not in the tested animal species.

5.1.2. Absorption, distribution, metabolism and excretion after exposure by other routes

Data on absorption, distribution, metabolism and excretion (ADME) following exposure by the dermal route shallbe provided where toxicity following dermal exposure is of concern compared to that following oral exposure. Before investigating ADME *in vivo* following dermal exposure, an *in vitro* dermal penetration study shall be conducted to assess the likely magnitude and rate of dermal bioavailability.

Absorption, distribution, metabolism and excretion after exposure by the dermal route shall be considered on the basis of the above information, unless the active substance causes skin irritation that would compromise the outcome of the study.

Dermal absorption estimation from data generated in these studies on the active substance shall be critically assessed for relevance to humans.

For volatile active substances (vapour pressure > 10^{-2} Pascal) absorption, distribution, metabolism and excretion after exposure by inhalation may be useful in human risk assessments.

5.2. Acute toxicity

The studies, data and information to be provided and evaluated shall be sufficient to permit the identification of effects following a single exposure to the active substance, and in particular to establish, or indicate:

(a) the toxicity of the active substance;
(b) the time course and characteristics of the effects with full details of behavioural changes, clinical signs, where evident, and possible gross pathological findings at post-mortem;
(c) the possible need to consider establishing acute reference doses (such as ARfD, aAOEL;
(d) where possible mode of toxic action;
(e) the relative hazard associated with the different routes of exposure.

While the emphasis shall be on estimating the toxicity ranges involved, the information generated shall also permit the active substance to be classified. The information generated through acute toxicity testing is of particular value in assessing hazards likely to arise in accident situations.

5.2.1. Oral

Circumstances in which required

The acute oral toxicity of the active substance shall always be reported.

5.2.2. Dermal

Circumstances in which required

The acute dermal toxicity of the active substance shall be reported unless waiving is scientifically justified (for example where oral LD_{50} is greater than 2 000 mg/kg). Both local and systemic effects shall be investigated.

Findings of severe skin irritation (Grade 4 erythema or oedema) in the dermal study shall be used instead of performing a specific irritation study.

5.2.3. Inhalation

Circumstances in which required

The acute inhalation toxicity of the active substance shall be reported where any of the following apply:
— the active substance has a vapour pressure > 1×10^{-2} Pa at 20 °C;
— the active substance is a powder containing a significant proportion of particles of a diameter < 50 μm (> 1 % on weight basis);
— the active substance is included in products that are powders or are applied by spraying. The

head/nose only exposure shall be used, unless whole body exposure can be justified.

5.2.4. Skin irritation

The results of the study shall provide information on the potential for skin irritancy of the active substance including, where relevant, the potential reversibility of the effects observed.

Before undertaking *in vivo* studies for corrosion/irritation of the active substance, a weight-of-evidence analysis shall be performed on the existing relevant data. Where insufficient data are available, they can be developed through application of sequential testing.
The testing strategy shall follow a tiered approach:
(1) the assessment of dermal corrosivity using a validated *in vitro* test method;
(2) the assessment of dermal irritation using a validated *in vitro* test method (such as human reconstituted skin models);
(3) an initial *in vivo* dermal irritation study using one animal, and where no adverse effects are noted;
(4) confirmatory testing using one or two additional animals.

Circumstances in which required

The skin irritancy study of the active substance shall always be provided. Where available, a dermal toxicity study shown not to produce irritation of the skin at the limit test dose level of 2 000 mg/kg body weight shall be used to waive the need for any dermal irritation studies.

5.2.5. Eye irritation

The results of the study shall provide the potential of eye irritancy of the active substance including, where relevant, the potential reversibility of the effects observed.

Before undertaking *in vivo* studies for eye corrosion/irritation of the active substance, a weight-of-evidence analysis shall be performed on the existing relevant data. Where available data are considered insufficient, further data may be developed through application of sequential testing.

The testing strategy shall follow a tiered approach:
(1) the use of an *in vitro* dermal irritation/corrosion test to predict eye irritation/corrosion;
(2) the performance of a validated or accepted *in vitro* eye irritation study to identify severe eye irritants/corrosives (such as Bovine Corneal Opacity and Permeability (BCOP) assay, Isolated Chicken Eye (ICE) assay, Isolated Rabbit Eye (IRE) assay, Hen's Egg Test - Chorio-Allantoic Membrane assay (HET-CAM)), and where negative results are obtained, the assessment of eye irritation using an *in vitro* test method for identification of non- irritants or irritants, and where not available;
(3) an initial *in vivo* eye irritation study using one animal, and where no adverse effects are noted;

(4) confirmatory testing using one or two additional animals.

Circumstances in which required

The eye irritancy of the active substance shall always be tested, except where it is likely that severe effects on the eyes may be produced based on criteria listed in the test methods.

5.2.6. Skin sensitisation

The study shall provide sufficient information to assess the potential of the active substance to provoke skin sensitisation reactions.

Circumstances in which required

The study shall always be carried out, except where the active substance is a known sensitiser. The local lymph node assay (LLNA) shall be used, including where appropriate the reduced variant of the assay. In case the LLNA cannot be conducted, a justification shall be provided and the Guinea Pig Maximisation Test shall be performed. Where a guinea pig assay (Maximisation or Buehler), meeting OECD guidelines and providing a clear result, is available, further testing shall not be carried out for animal welfare reasons.

Since an active substance identified as a skin sensitiser can potentially induce hypersensitivity reaction, potential respiratory sensitisation should be taken into account when appropriate tests are available or when there are indications of respiratory sensitisation effects.

Phototoxicity

The study shall provide information on the potential of certain active substances to induce cytotoxicity in combination with light, for example active substances that are phototoxic *in vivo* after systemic exposure and distribution to the skin, as well as active substances that act as photoirritants after dermal application. A positive result shall be taken into account when considering potential human exposure.

Circumstances in which required

The *in vitro* study shall be required where the active substance absorbs electromagnetic radiation in the range 290- 700 nm and is liable to reach the eyes or light-exposed areas of skin, either by direct contact or through systemic distribution.

If the Ultraviolet/visible molar extinction/absorption coefficient of the active substance is less than 10 $L \times mol^{-1} \times cm^{-1}$, no toxicity testing is required.

5.3. Short-term toxicity

Short-term toxicity studies shall be designed to provide information as to the amount of the active substance that can be tolerated without adverse effects under the conditions of the study and to elucidate health hazards occurring at higher dose levels. Such studies provide useful data on the risks for those handling and using VPPs containing the active substance, among other possible exposed groups. In particular, short-term studies provide an essential insight into possible repeated actions of the active substance and the risks to humans who may be exposed. In addition short-term studies provide information useful in the design of chronic toxicity studies.

The studies, data and information to be provided and evaluated, shall be sufficient to permit the identification of effects following repeated exposure to the active substance, and in particular to further establish, or indicate:

(a) the relationship between dose and adverse effects;
(b) toxicity of the active substance including where possible the No Observed Adverse Effect Level (NOAEL);
(c) target organs, where relevant (including immune, nervous and endocrine systems);
(d) the time course and characteristics of adverse effects with full details of behavioural changes and possible pathological findings at post-mortem;
(e) specific adverse effects and pathological changes produced;
(f) where relevant the persistence and reversibility of certain adverse effects observed, following discontinuation of dosing;
(g) where possible, the mode of toxic action;
(h) the relative hazard associated with the different routes of exposure;
(i) relevant critical endpoints at appropriate time points for setting reference values, where necessary.

Toxicokinetic data (that is to say blood concentration) shall be included in short term studies. In order to avoid increased animal use, the data may be derived in range finding studies.

If nervous system, immune system or endocrine system are specific targets in short term studies at dose levels not producing marked toxicity, supplementary studies, including functional testing, shall be carried out (see point 5.8.2).

5.3.1. Oral 28-day study

Circumstances in which

required

Where available, 28-day studies shall be

reported.

5.3.2. Oral 90-day study

Circumstances in which required

The short-term oral toxicity of the active substance to rodents (90-day), usually the rat, a different rodent species shall be justified, and non rodents (90-day toxicity study in dogs), shall always be reported.

In the 90-day study, potential neurotoxic and immunotoxic effects, genotoxicity by way of micronuclei formation and effects potentially related to changes in the hormonal system shall be carefully addressed.

5.3.3. Other routes

Circumstances in which required

For human risk assessment additional dermal studies shall be considered on a case by case basis, unless the active substance is a severe irritant.

For volatile active substances (vapour pressure $>10^{-2}$ Pascal) expert judgement (for example based on route-specific kinetic data) shall be required to decide whether the short term studies have to be performed by inhalation exposure.

5.4. Genotoxicity testing

The aim of genotoxicity testing shall be to:
— predict genotoxic potential,

— identify genotoxic carcinogens at an early stage,
— elucidate the mechanism of action of some carcinogens.

Appropriate dose levels, depending on the test requirements, shall be used in either *in vitro* or *in vivo* assays. A tiered approach shall be adopted, with selection of higher tier tests being dependent upon interpretation of results at each stage.

Special testing requirements in relation to photomutagenicity may be indicated by the structure of a molecule. If the Ultraviolet/visible molar extinction/absorption coefficient of the active substance and its major metabolites is less than 1 000 L × mol^{-1} × cm^{-1}, photomutagenicity testing is not required.

5.4.1. In vitro *studies*

Circumstances in which required

The following *in vitro* mutagenicity tests shall be performed: bacterial assay for gene mutation, combined test for structural and numerical chromosome aberrations in mammalian cells and test for gene mutation in mammalian cells.

However, if gene mutation and clastogenicity/aneuploidy are detected in a battery of tests consisting of Ames and *in vitro* micronucleus (IVM), no further *in vitro* testing needs to be conducted.

If there are indications of micronucleus formation in an *in vitro* micronucleus assay further testing with appropriate staining procedures shall be conducted to clarify if there is an aneugenic or clastogenic response. Further inves- tigation of the aneugenic response may be considered to determine whether there is sufficient evidence for a threshold mechanism and threshold concentration for the aneugenic response (particularly for non-disjunction).

Active substances which display highly bacteriostatic properties as demonstrated in a range finding test shall be tested in two different *in vitro* mammalian cell tests for gene mutation. Non performance of the Ames test shall be justified.

For active substances bearing structural alerts that have given negative results in the standard test battery, additional testing may be required if the standard tests have not been optimised for these alerts. The choice of additional study or study plan modifications depends on the chemical nature, the known reactivity and the metabolism data on the structurally alerting active substance.

5.4.2. In vivo *studies in somatic cells*

Circumstances in which required

If all the results of the *in vitro* studies are negative, at least one *in vivo* study shall be done with demonstration of exposure to the test tissue (such as cell toxicity or toxicokinetic data), unless valid *in vivo* micronucleus data are generated within a repeat dose study and the *in vivo* micronucleus test is the appropriate test to be conducted to address this information requirement.

A negative result in the first *in vivo* test in somatic cells shall provide sufficient reassurance for active substances that are negative in the three *in vitro* tests.

For active substances for which an equivocal or a positive test result is obtained in any *in vitro* test, the nature of additional testing needed shall be considered on a case-by-case basis taking into account all relevant information using the same endpoint as in the *in vitro* test.

If the *in vitro* mammalian chromosome aberration test or the *in vitro* micronucleus test is positive for

clastogenicity, an *in vivo* test for clastogenicity using somatic cells such as metaphase analysis in rodent bone marrow or micronucleus test in rodents shall be conducted.

If the *in vitro* micronucleus test for numerical chromosome aberrations on mammalian cells is positive or the *in vitro* mammalian chromosome test is positive for numerical chromosome changes, an *in vivo* micronucleus test shall be conducted. In case of positive result in the *in vivo* micronucleus assay, appropriate staining procedure such as fluorescence in-situ hybridisation (FISH) shall be used to identify an aneugenic and/or clastogenic response.

If either of the *in vitro* gene mutation tests is positive, an *in vivo* test to investigate the induction of gene mutation shall be conducted, such as the Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay.

When conducting *in vivo* genotoxicity studies, only relevant exposure routes and methods (*such as* admixture to diet, drinking water, skin application, inhalation and gavage) shall be used. There shall be convincing evidence that the relevant tissue will be reached by the chosen exposure route and application method. Other exposure tech- niques (*such as* intraperitoneal or subcutaneous injection) that are likely to result in abnormal kinetics, distribution and metabolism shall be justified.

Consideration shall be given to conducting an *in vivo* test as part of one of the short-term toxicity studies described under point 5.3.

5.4.3. In vivo *studies in germ cells*

Circumstances in which required

The necessity for conducting these tests shall be considered on a case by case basis, taking into account information regarding toxicokinetics, use and anticipated exposure.

For most of the active substances recognised as *in vivo* somatic cell mutagens no further genotoxicity testing shall be necessary since they will be considered to be potential genotoxic carcinogens and potential germ cell mutagens.

However, in some specific cases germ cells studies may be undertaken to demonstrate whether a somatic cell mutagen is or is not a germ cell mutagen.

The type of mutation produced in earlier studies namely gene, numerical chromosome or structural chromosome changes, shall be considered when selecting the appropriate assay.

A study for the presence of DNA adducts in gonad cells may also be considered.

5.5. Long-term toxicity and carcinogenicity

The results of the long-term studies conducted and reported, taken together with other relevant data and information on the active substance, shall be sufficient to permit the identification of effects, following repeated exposure to the active substance, and in particular shall be sufficient to:
— identify adverse effects resulting from long-term exposure to the active substance,
— identify target organs, where relevant,
— establish the dose-response relationship,
— establish the NOAEL and, if necessary, other appropriate reference points.

Correspondingly, the results of the carcinogenicity studies taken together with other relevant data and information on the active substance, shall be sufficient to permit the evaluation of hazards for humans, following repeated exposure to the active substance, and in particular shall be sufficient:
(a) to identify carcinogenic effects resulting from long-term exposure to the active substance;

to establish the species, sex, and organ specificity of tumours induced;

(b) to establish the dose-response relationship;

(c) where possible, to identify the maximum dose eliciting no carcinogenic effect;

(d) where possible, to determine the mode of action and human relevance of any identified carcinogenic response.

Circumstances in which required

The long-term toxicity and carcinogenicity of all active substances shall be determined. If in exceptional circum- stances it is claimed that such testing is unnecessary, that claim shall be fully justified.

Test conditions

A long-term oral toxicity study and a long-term carcinogenicity study (two years) of the active substance shall be conducted using rat as test species; where possible these studies shall be combined.

A second carcinogenicity study of the active substance shall be conducted using mouse as test species, unless it can be scientifically justified that this is not necessary. In such cases, scientifically validated alternative carcinogenicity models may be used instead of a second carcinogenicity study.

If comparative metabolism data indicate that either rat or mouse is an inappropriate model for human cancer risk assessment, an alternative species shall be considered.

Experimental data, including the elucidation of the possible mode of action involved and relevance to humans, shall be provided where the mode of action for carcinogenicity is considered to be non-genotoxic.

Where submitted, historical control data shall be from the same species and strain, maintained under similar conditions in the same laboratory and shall be from contemporaneous studies. Additional historical control data from other laboratories may be reported separately as supplementary information.

The information on historical control data provided shall include:

(a) identification of species and strain, name of the supplier, and specific colony identification, if the supplier has more than one geographical location;

(b) name of the laboratory and the dates when the study was performed;

(c) description of the general conditions under which animals were maintained, including the type or brand of diet and, where possible, the amount consumed;

(d) approximate age, in days, and weight of the control animals at the beginning of the study and at the time of killing or death;

(e) description of the control group mortality pattern observed during or at the end of the study, and other pertinent observations (such as diseases, infections);

(f) name of the laboratory and the examining scientists responsible for gathering and interpreting the pathological data from the study;

(g) a statement of the nature of the tumours that may have been combined to produce any of the incidence data.

The historical control data shall be presented on a study by study basis giving absolute values plus percentage and relative or transformed values where these are helpful in the evaluation. If combined or summary data are submitted, these shall contain information on the range of values, the mean, median and, if applicable, standard deviation.

The doses tested, including the highest dose tested, shall be selected on the basis of the results of short-term testing and where available at the time of planning the studies concerned, on the basis of

metabolism and toxicokinetic data. Dose selection should consider toxicokinetic data such as saturation of absorption measured by systemic availability of active substance and/or metabolites.

Doses, causing excessive toxicity shall not be considered relevant to evaluations to be made. Determination of blood concentration of the active substance (for example around T_{max}) shall be considered in long-term studies.

In the collection of data and compilation of reports, incidence of benign and malignant tumours shall not be combined. Dissimilar, un-associated tumours, whether benign or malignant, occurring in the same organ, shall not be combined for reporting purposes.

In the interests of avoiding confusion, conventional histopathological terminology commonly used when the study is conducted such as that published by the International Agency for Research on Cancer shall be used in the nomenclature and reporting of tumours. The system used shall be identified.

Biological material selected for histopathological examination shall include material selected to provide further information on lesions identified during gross pathological examination. Where relevant to the elucidation of mechanism of action and available, special histological (staining) techniques, histochemical techniques and electron microscopic examinations, might be of value, and when conducted, shall be reported.

5.6. Reproductive toxicity

Possible effects on reproductive physiology and the development of progeny shall be investigated and reported concerning the following aspects:

- Impairment of male and female reproductive functions or capacity, for example from effects on oestrus cycle, sexual behaviour, any aspect of spermatogenesis or oogenesis, or hormonal activity or physiological response which would interfere with the capacity to fertilise, fertilisation itself or development of the fertilised ovum up to and including implantation.
- Harmful effects on the progeny, for example any effect interfering with normal development, both before and after birth. This includes morphological malformations such as anogenital distance, nipple retention, and functional disturbances (such as reproductive and neurological effects).

Effects accentuated over generations shall be reported.

The active substance and its relevant metabolites shall be measured in milk as a second tier investigation where relevant effects are observed in the offspring or are expected (for example from a range-finding study).

Potential neurotoxic, immunotoxic effects and effects potentially related to changes in the hormonal system shall be carefully addressed and reported.

Investigations shall take account of all available and relevant data, including the results of general toxicity studies if relevant parameters (such as semen analysis, oestrous cyclicity, reproductive organ histopathology) are included, as well as knowledge concerning structural analogues to the active substance.

While the standard reference point for treatment responses shall be concurrent control data, historical control data may be helpful in the interpretation of particular reproductive studies. Where submitted, historical control data shall be from the same species and strain, maintained under similar conditions in the same laboratory and shall be from contemporaneous studies.

The information on historical control data provided shall include:

(a) identification of species and strain, name of the supplier, and specific colony identification, if the supplier has more than one geographical location;
(b) name of the laboratory and the dates when the study was performed;
(c) description of the general conditions under which animals were maintained, including the type or brand of diet and, where possible, the amount consumed;
(d) approximate age, in days, and weight of the control animals at the beginning of the study and at the time of killing or death;
(e) description of the control group mortality pattern observed during or at the end of the study, and other pertinent observations (such as diseases, infections);

(f) Name of the laboratory and the examining scientists responsible for gathering and interpreting the pathological data from the study.

The historical control data shall be presented on a study by study basis giving absolute values plus percentage and relative or transformed values where these are helpful in the evaluation. If combined or summary data are submitted, these shall contain information on the range of values, the mean, median and, if applicable, standard deviation.

In order to provide useful information in the design and interpretation of developmental toxicity studies, information on blood concentration of the active substance in parents and foetus/offspring may be included in higher tier studies and reported.

5.6.1. Generational studies

The generational studies reported, taken together with other relevant data and information on the active substance, shall be sufficient to permit the identification of effects for reproduction, following repeated exposure to the active substance, and in particular shall be sufficient:
(a) to identify direct and indirect effects on reproduction resulting from exposure to the active substance;
(b) to identify any non-reproductive adverse effects occurring at lower doses than in short-term and chronic toxicity testing;
(c) to establish the NOAELs for parental toxicity, reproductive outcome and pup development.

Circumstances in which required

A reproduction toxicity study in rats over at least two generations shall be reported.

The OECD extended one-generation reproductive toxicity study may be considered as an alternative approach to the multi-generation study.

Where necessary for a better interpretation of the effects on reproduction and as far as this information is not yet available, supplementary studies may be required to provide information on the affected gender and the possible mechanisms.

5.6.2. Developmental toxicity studies

The developmental toxicity studies reported, taken together with other relevant data and information on the active substance, shall be sufficient to permit the assessment of effects on embryonic and foetal development, following repeated exposure to the active substance, and in particular shall be sufficient:
(a) to identify direct and indirect effects on embryonic and foetal development resulting from exposure to the active substance;
(b) to identify any maternal toxicity;
(c) to establish the relationship between observed responses and dose in both dam and offspring;
(d) to establish NOAELs for maternal toxicity and pup development;

(e) to provide additional information on adverse effects in pregnant as compared with non-pregnant females;
(f) to provide additional information on any enhancement of general toxic effects of pregnant animals.

Circumstances in which required Developmental toxicity studies shall always be carried out.

Tests conditions

Developmental toxicity shall be determined for rat and rabbit by the oral route; the rat study shall not be conducted if developmental toxicity has been adequately assessed as part of an extended one-generation repro- ductive toxicity study.

Additional routes may be useful in human risk assessment. Malformations and variations shall be reported separately and combined in such a way that all relevant changes which are observed to occur in characteristic patterns in individual foetuses or those that can be considered to represent different grades of severity of the same type of change are reported in a concise manner.

Diagnostic criteria for malformations and variations shall be given in the report. The glossary of terminology under development by the International Federation of Teratology Societies shall be considered where possible.

When indicated by observations in other studies or the mode of action of the test substance, supplementary studies or information may be required to provide information on the postnatal manifestation of effects such as devel- opmental neurotoxicity.

5.7. Neurotoxicity studies

5.7.1. Neurotoxicity studies in rodents

Neurotoxicity studies in rodents shall provide sufficient data to evaluate the potential neurotoxicity of the active substance (neurobehavioural and neuropathological effects) after single and repeated exposure.

Circumstances in which required

Such studies shall be performed for active substances with structures that are similar or related to those capable of inducing neurotoxicity, and for active substances which induce specific indications of potential neurotoxicity, neurological signs or neuropathological lesions in toxicity studies at dose levels not associated with marked general toxicity. Performance of such studies shall also be considered for substances with a neurotoxic mode of pesticidal action.

Consideration shall be given to including neurotoxicity investigations in routine toxicology studies.

5.7.2. Delayed polyneuropathy studies

Delayed polyneuropathy studies shall provide sufficient data to evaluate if the active substance may provoke delayed polyneuropathy after acute and repeated exposure. A repeated exposure study may be waived unless there are indications that the compound accumulates and significant inhibition of neuropathy target esterase or clinical/histopathological signs of delayed polyneuropathy occur at around the hen LD_{50} as determined in the single dose test.

Circumstances in which required

These studies shall be performed for active substances of similar or related structures to those capable

of inducing delayed polyneuropathy such as organophosphorus compounds.

5.8. Other toxicological studies

5.8.1. Toxicity studies of metabolites

Supplementary studies, where they relate to substances other than the active substance, are not a routine requirement. Decisions as to the need for supplementary studies shall be made on a case by case basis.

Where as a result of metabolism or other processes, metabolites from plants or in animal products, soil, ground- water, open air differ from those in animals used for the toxicology studies or are detected in low proportions in animals, further testing shall be carried out on a case by case basis, taking into account the amount of metabolite and the chemical structure of the metabolite compared to the parent.

5.8.2. Supplementary studies on the active substance

Supplementary studies shall be carried out where they are necessary to further clarify observed effects taking into account the results of the available toxicological and metabolism studies and the most important exposure routes. Such studies may include:

(a) studies on absorption, distribution, excretion and metabolism, in a second species;

(b) studies on the immunotoxicological potential;

(c) a targeted single dose study to derive appropriate acute reference values (ARfD, aAOEL);

(d) studies on other routes of administration;

(e) studies on the carcinogenic potential;

(f) studies on mixture effects.

Studies required shall be designed on an individual basis, in the light of the particular parameters to be investigated and the objectives to be achieved.

5.8.3. Endocrine disrupting properties

If there is evidence that the active substance may have endocrine disrupting properties, additional information or specific studies shall be required:
— to elucidate the mode/mechanism of action,
— to provide sufficient evidence for relevant adverse effects.

Studies required shall be designed on an individual basis and taking into account Union or internationally agreed guidelines, in the light of the particular parameters to be investigated and the objectives to be achieved.

5.9. Medical data

Practical data and information relevant to the recognition of the symptoms of poisoning and on the effectiveness of first aid and therapeutic measures shall be submitted. Such data and information shall include reports of any studies investi- gating antidote pharmacology or safety pharmacology. Where relevant, the effectiveness of potential antagonists to poisoning shall be investigated and reported.

Data and information relevant to the effects of human exposure, where available, shall be used to confirm the validity of extrapolations made and conclusions reached with respect to target organs,

dose-response relationships, and the reversibility of adverse effects. Such data may be generated following accidental, occupational exposure or incidents of intentional self-poisoning, and shall be reported if available.

5.9.1. Medical surveillance on manufacturing plant personnel and monitoring studies

Reports of occupational health surveillance programs and of monitoring studies shall be submitted, supported with detailed information on the design of the programme, the number of exposed persons included in the programme, the nature of their exposure to the active substance, and their exposure to other potentially hazardous agents. Such reports shall, where feasible, include data relevant to the mechanism of action of the active substance. These reports shall, where available, include data from persons exposed in manufacturing plants, or during or after application of the active substance (for example from monitoring studies in operators, workers, residents, bystanders or victims of accidents). Available information on adverse health effects including allergenic responses in workers and others exposed to the active substance, shall be provided, and include where relevant details of any incident. The information provided shall, where available, include details of frequency, level and duration of exposure, symptoms observed and other relevant clinical information.

5.9.2. Data collected on humans

Where available, reports from studies with humans, such as tests on toxicokinetics and metabolism, or tests on skin irritation or skin sensitisation, shall be submitted.

In general, the reference values shall be based on animal studies, but if appropriate scientifically valid and ethically generated human data are available and show that humans are more sensitive and lead to lower regulatory limit values, these data shall take precedence over animal data.

5.9.3. Direct observations

Available reports from the open literature, relating to clinical cases and poisoning incidents, where they are from refereed journals or official reports, shall be submitted together with reports of any follow-up studies undertaken. Such reports shall, where available, contain complete descriptions of the nature, level and duration of exposure, as well as the clinical symptoms observed, first aid and therapeutic measures applied and measurements and obser- vations made.

Where supported with the necessary level of detail, such documentation shall be used to confirm the validity of extrapolations from animal data to man and to identify unexpected adverse effects which are specific to humans.

5.9.4. Epidemiological studies

Relevant epidemiological studies shall be submitted, where available.

5.9.5. Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests

Where available, detailed description of the clinical signs and symptoms of poisoning, including the early signs and symptoms and full details of clinical tests useful for diagnostic purposes shall be provided including full details of the time courses involved relevant to the ingestion, dermal exposure or inhalation of varying amounts of the active substance.

5.9.6. Proposed treatment: first aid measures, antidotes, medical treatment

First aid measures to be used in the event of poisoning (actual and suspected) and in the event of contamination of eyes shall be provided. Therapeutic regimes for use in the event of poisoning or contamination of eyes, including where available the use of antidotes, shall be described in full.

Information based on practical experience, where it exists and is available, in other cases on theoretical grounds, as to the effectiveness of alternative treatment regimes, where relevant, shall be provided. Contraindications associated with particular regimes, particularly those relating to 'general medical problems' and conditions, shall be described.

5.9.7. Expected effects of poisoning

Where known, the expected effects and the duration of these effects following poisoning shall be described. That description shall include the impact of:

— the type, level and duration of exposure, or ingestion, and

— varying time periods between exposure, or ingestion, and commencement of treatment.

PART A: SECTION 6

RESIDUES IN FOOD AND FEED

6.1. Storage stability of residues

Studies concerning storage stability of residues shall investigate the stability of residues products of animal origin during storage prior to analysis.

Circumstances in which required

Provided that samples are frozen within 24 hours after sampling and unless a compound is otherwise known to be volatile or labile, stability data shall not be required for samples extracted and analysed within 30 days from sampling (six months in the case of radio-labelled material).

The stability of extracts shall be investigated if extracts are not analysed immediately.

Test conditions

Studies with non-radio-labelled active substances shall be carried out with representative substrates. They may be either performed on samples from treated crops or animals with incurred residues or by fortification experiments. In the latter case, aliquots of prepared control samples shall be spiked with a known amount of chemical before storage under normal storage conditions.

The studies shall address stability of individual components of the residue definition relevant to risk assessment, which may require spiking different samples with different analytes. In case of different analytical targets (for example targeting either single compounds or a common moiety) more than one set of storage stability data may be needed.

The duration of the stability studies shall be suitable to address the length over which the samples or extracts have been stored in the corresponding studies.

Detailed information with respect to the sample preparation and storage conditions (temperature and duration) of samples and extracts shall be submitted. Where the degradation during storage is significant (more than 30%) a change in the storage conditions or not storing the samples prior to analysis shall be considered. All studies where unsatisfactory storage conditions were used shall be repeated.

Storage stability data using sample extracts shall also be required unless samples are analysed within 24 hours of extraction.

Results shall be presented as absolute values in mg/kg and not adjusted by recovery, as well as percentage of nominal spike value.

6.2. Proposed residue definitions and maximum residue levels

6.7.1. Proposed residue definitions

The following elements shall be considered when judging which compounds are to be included in the residue definition:
— the toxicological significance of the compounds,
— the amounts likely to be present, and
— the analytical methods proposed for post-approval control and monitoring purposes.

Two different residue definitions may be needed: one for enforcement purposes, based on the marker concept, and one for risk assessment purposes, taking into account toxicologically relevant compounds.

Analytical work in residue trials shall cover all the components of the residue definition for risk assessment.

Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed

A maximum residue level shall be provided for all products of animal origin. In cases where the limits are not determined a guideline level, that is to say a level derived on the same principles used for MRL setting, shall be provided.

For processed products processing factors shall be provided, unless no processing studies are required.

Furthermore, supervised trials median residue (STMR) and highest residue (HR) values shall be derived and, in cases where processing factors are proposed, STMR-P and HR-P values.

6.7.2. Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed for imported products (import tolerance)

Point 6.7.2 shall apply to MRLs proposed for imported products (import tolerances).

6.3. Other studies

6.10.1. *Residue level in pollen and bee products*

The objective of these studies shall be to determine the residue in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom.

The type and conditions of the studies to be performed shall be discussed with the national competent authorities.

PART A: SECTION 7

FATE AND BEHAVIOUR IN THE ENVIRONMENT

7.1. Fate and behaviour in soil

All relevant information on the type and the properties of the soil used in the studies, including pH, organic carbon content, particle size distribution and water holding capacity shall be reported.

The microbial biomass of soils used for laboratory degradation studies shall be determined immediately before the commencement and at the end of the study.

The soils used for degradation, adsorption and desorption or mobility studies shall be representative of the range of agricultural soils typical of the various regions of the Union where use exists or is anticipated.

The soils shall fulfil the following conditions:

-- they shall cover a range of organic carbon content, particle size distribution and $pH_{(preferably\ CaCl2)}$ values, and

— where on the basis of other information, degradation or mobility are expected to be pH dependent, for example solubility and hydrolysis rate (see points 2.7 and 2.8), they shall cover approximately the following $pH_{(preferably\ CaCl2)}$ ranges: 5 to 6, 6 to 7 and 7 to 8.

Soils used shall, wherever possible, be freshly sampled. If use of stored soils is unavoidable, storage shall be carried out for a limited time (at the most three months) under defined and reported conditions, which are adequate to maintain soil microbial viability. Soils stored for longer periods of time may only be used for adsorption/desorption studies.

A soil having extreme characteristics with respect to parameters such as particle size distribution, organic carbon content and pH shall not be used.

Field studies shall be carried out in conditions as close to normal agricultural practice as possible on a range of soils and climatic conditions representative of the areas of use. Weather conditions shall be reported in cases where field studies are conducted.

7.1.1. Route of degradation in soil

The data and information provided, together with other relevant data and information, shall be sufficient to:

(a) identify, if possible, the relative importance of the types of processes involved (balance between chemical and biological degradation);

(b) identify the individual components present which at any time account for more than 10 % of the amount of active substance added, including, if possible, non-extractable residues;

(c) identify, if possible, the individual components which in at least two sequential measurements, account for more than 5 % of the amount of active substance added;

(d) identify, if possible, the individual components (> 5 %) for which at the end of the study the maximum of formation is not yet reached;

(e) identify or characterise, if possible, other individual components present;

(f) establish the relative proportions of the components present (mass balance); and

(g) permit the soil residue of concern to which non-target species are or may be exposed, to be defined.

For the purposes of this Section non-extractable residues means chemical species originating from active substances contained in finished product used in accordance with good agricultural practice that cannot be extracted by methods which do not significantly change the chemical nature of these residues or the nature of the soil matrix. These non-extractable residues are not considered to include fragments through metabolic pathways leading to natural products.

7.1.1.1. Aerobic degradation

Circumstances in which required

The pathway or pathways of aerobic degradation shall be reported except where the nature and manner of use of finished product containing the active substance precludes soil contamination.

Test Conditions

Studies on the degradation pathway or pathways shall be reported for at least one soil. Oxygen levels shall be maintained at levels that do not restrict micro-organisms ability to metabolise aerobically. If there is reason to believe that the route of degradation is dependent on one or more properties of the soil, such as pH or clay content, the route of degradation shall be reported for at least one additional soil for which dependent properties are different.

Results obtained shall be presented in the form of schematic drawings showing the pathways involved, and in the form of balance sheets which show the distribution of radio-label as a function of time, as between:

(a) active substance;

(b) CO_2;

(c) volatile compounds other than CO_2;

(d) individual identified transformation products referred to in point 7.1.1;

(e) extractable substances not identified; and

(f) non-extractable residues in soil.

The investigation of degradation pathways shall include all possible steps to characterise and quantify non- extractable residues formed after 100 days when exceeding 70 % of the applied dose of the active substance. The techniques and methodologies applied shall be selected on a case-by-case basis. A justification shall be provided where the compounds involved are not characterised.

The duration of the study shall be at least 120 days, except where after a shorter period the levels of non- extractable residues and CO_2 are such that they can be extrapolated in a reliable way to 100 days. It shall be longer where this is necessary to establish the degradation pathway of the active substance and its metabolites, breakdown or reaction products.

7.1.1.2. Anerobic degradation

Circumstances in which required

An anaerobic degradation study shall be submitted unless the applicant shows that exposure of the finished product containing the active substance to anaerobic conditions is unlikely to occur for the intended uses.

Test conditions

Point 7.1.1.1 shall apply as regards test conditions except oxygen levels which shall be minimised as to ensure that micro-organisms metabolise anaerobically.

7.1.2. Rate of degradation in soil

7.1.2.1. Laboratory studies

Laboratory studies on soil degradation shall provide best possible estimates of the time required for degradation of 50 % and 90 % ($DegT50_{lab}$ and $DegT90_{lab}$) of the active substance, its metabolites, breakdown and reaction products under laboratory conditions.

7.1.2.1.1. Aerobic degradation of the active substance

Circumstances in which required

The rate of degradation in soil shall be reported, except where the nature and manner of use of finished product containing the active substance preclude soil contamination.

Test conditions

Studies on the rate of aerobic degradation of the active substance shall be reported for three soils in addition to the one required under point 7.1.1.1. Reliable DegT50 and 90 values shall be available for a minimum of four different soils.

The duration of the study shall be at least 120 days. It shall be longer where this is necessary to establish the kinetic formation fractions of the metabolites, breakdown or reaction products. If more than 90 % of the active substance is degraded before the period of 120 days expires, the test duration may be shorter.

In order to assess the influence of temperature on degradation, a calculation with an adequate Q10 factor or an adequate number of additional studies at a range of temperatures shall be performed.

Aerobic degradation of metabolites, breakdown and reaction products

Circumstances in which required

Aerobic degradation (DegT50 and 90 values) from a minimum of three different soils shall be provided for metabolites, breakdown and reaction products which occur in soil if one of the following conditions is fulfilled:

(a) they account for more than 10 % of the amount of active substance added at any time during the studies;

(b) they account for more than 5 % of the amount of active substance added in at least two sequential measurements;

(c) the maximum of formation is not reached at the end of the study but accounts for at least 5 % of the active substance at the final measurement;

(d) all metabolites found in lysimeter studies at annual average concentrations exceed 0.1 µg/L in the leachate.

Studies shall not be required where three DegT50 and 90 values can be reliably determined from the results of the degradation studies where the active substance is applied as test substance.

Test conditions

Test conditions shall be those indicated in Section 7.1.2.1.1 except the test substance applied will be the metabolite, breakdown or reaction product. Studies on metabolites, breakdown and reaction products shall be provided where these are necessary to obtain reliable DegT50 and 90 values for at least three different soils.

7.1.2.1.2. Anaerobic degradation of the active substance

Circumstances in which required

The rate of anaerobic degradation of the active substance shall be reported where an anaerobic study has to be performed in accordance with point 7.1.1.2.

Test conditions

Anaerobic DegT50 and 90 values for the active substance are needed for the test conditions outlined in point 7.1.1.2.

7.1.2.1.3. Anaerobic degradation of metabolites, breakdown and reaction products

Circumstances in which required

Anaerobic degradation studies shall be provided for metabolites, breakdown and reaction products which occur in soil if they fulfil one of the following conditions:

(a) at any time during the studies account for more than 10 % of the amount of active substance added;

(b) in at least two sequential measurements account for more than 5 % of the amount of active substance added, if feasible;

(c) at the end of the study the maximum of formation is not yet reached but accounts for at least 5 % of the active substance at the final measurement, if feasible.

The applicant may deviate from such requirement by showing that DegT50 values for metabolites, breakdown and reaction products can be reliably determined from the results of the anaerobic degradation studies with the active substance.

Test conditions

Studies on metabolites, breakdown and reaction products shall be provided for one soil for the test conditions outlined at point 7.1.1.2.

7.1.2.2. Field studies

7.1.2.2.1. Soil dissipation studies

The soil dissipation studies shall provide estimates of the time required for dissipation of 50 % and 90 % ($DisT50_{field}$ and $DisT90_{field}$) and, if possible, of the time required for degradation of 50 % and 90 % ($DegT50_{field}$ and $DegT90_{field}$), of the active substance under field conditions. Where relevant, information on metabolites, breakdown and reaction products shall be provided.

Circumstances in which required

Such studies shall be conducted for the active substance, its metabolites, breakdown and reaction products if one of the following conditions is fulfilled:

(a) $DegT50_{lab}$ for active substance, $DegT50_{lab}$ or $DisT50_{lab}$ for metabolites, breakdown and reaction products, in one or more soils determined at 20 °C and at a moisture content of the soil related to a pF value of 2 (suction pressure) is greater than 60 days; or

(b) $DegT90_{lab}$ for active substance, $DegT90_{lab}$ or $DisT90_{lab}$ for metabolites, breakdown and reaction products, in one or more soils determined at 20 °C and at a moisture content of the soil related to a pF value of 2 (suction pressure) is greater than 200 days.

If during field studies metabolites, breakdown and reaction products which are present in laboratory

studies are below the lowest technically feasible LOQ, which shall not exceed an equivalent of 5 % (molar basis) of the nominal concentration of active ingredient applied, no additional information on the fate and behaviour of these compounds shall be provided. In those cases, a scientifically valid justification for any discrepancy between laboratory and field appearance of metabolites shall be provided.

Test conditions

Individual studies on a range of representative soils (normally at least four different types at different geographical locations) shall be continued until at least 90% of the amount applied has dissipated from the soil or been transformed to substances that are not the subject of the investigation.

7.1.2.2.2. Soil accumulation studies

Soil accumulation studies shall provide sufficient information to evaluate the possibility of accumulation of residues of the active substance and of metabolites, breakdown and reaction products. The soil accumulation studies shall provide estimates of the time required for dissipation of 50 % and 90 % ($DisT50_{field}$ and $DisT90_{field}$) and, if possible, shall provide estimates of the time required for degradation of 50 % and 90 % ($DegT50_{field}$ and $DegT90_{field}$), of the active substance under field conditions.

Circumstances in which required

Where on the basis of soil dissipation studies it is established that $DisT90_{field}$, in one or more soils, is greater than one year and where repeated application is envisaged, whether in the same growing season or in succeeding years, the possibility of accumulation of residues in soil and the level at which a plateau concen- tration is achieved shall be investigated except where reliable information can be provided by a model calculation or another appropriate assessment.

Test conditions

Long-term field studies shall be performed on at least two relevant soils at different geographical locations and involve multiple applications.

7.1.3. Adsorption and desorption in soil

7.1.3.1. Adsorption and desorption

The information provided, together with other relevant data, shall be sufficient to establish the adsorption coefficient of the active substance and of its metabolites, breakdown and reaction products.

Adsorption and desorption of the active substance

Circumstances in which required

Studies on adsorption and desorption of the active substance shall be provided, except where the nature and manner of use of final product containing the active substance preclude.

Test conditions

Studies on the active substance shall be reported for at least four soils.

Where the batch equilibrium method cannot be applied due to fast degradation, methods such

as studies with short equilibration times, QSPR (Quantitative Structure Property Relationship) or the HPLC (High-Performance Liquid Chromatography) method shall be considered as possible alternatives. Where the batch equilibrium method cannot be applied due to weak adsorption, column leaching studies (see point 7.1.4.1) shall be considered as an alternative.

7.1.3.1.1. Adsorption and desorption of metabolites, breakdown and reaction products

Circumstances in which required

Studies on adsorption and desorption shall be provided for all metabolites, breakdown and reaction products, for which in soil degradation studies one of the following conditions is fulfilled:

(a) they account for more than 10 % of the amount of active substance added, at any time during the studies;

(b) they account for more than 5 % of the amount of active substance added in at least two sequential measurements;

(c) the maximum of formation is not reached at the end of the study but accounts for at least 5 % of the active substance at the final measurement;

(d) all metabolites found in lysimeter studies at annual average concentrations exceeding 0,1 μg/L in the leachate.

Test conditions

Studies on metabolites, breakdown and reaction products shall be provided for at least three soils.

Where the batch equilibrium method cannot be applied due to fast degradation, methods such as studies with short equilibration times, QSPR or the HPLC method shall be considered as an alternative. Where the batch equilibrium method cannot be applied due to weak adsorption, column leaching studies (see point 7.1.4.1) shall be considered as an alternative.

7.1.3.2. Aged sorption

As a higher tier option, information on aged sorption may be provided.

7.1.4. Mobility in soil

7.1.4.1. Column leaching studies

7.1.4.1.1. Column leaching of the active substance

Column leaching studies shall provide sufficient data to evaluate the mobility and leaching potential of the active substance.

Circumstances in which required

Studies in at least four soils shall be carried out where in the adsorption and desorption studies provided for under point 7.1.2 it is not possible to obtain reliable adsorption coefficient values due to weak adsorption (such as Koc < 25 L/Kg).

7.1.4.1.2. Column leaching of metabolites, breakdown and reaction products

The test shall provide sufficient data to evaluate the mobility and leaching potential of metabolites,

breakdown and reaction products.

Circumstances in which required

Studies in at least three soils shall be carried out where in the adsorption and desorption studies provided for under point 7.1.2 it is not possible to obtain reliable adsorption coefficient values due to weak adsorption (such as Koc < 25 L/Kg).

7.1.4.2. Lysimeter studies

Lysimeter studies shall be performed, where necessary, to provide information on:

— the mobility in soil,

— the potential for leaching to ground water,

— the potential distribution in soil.

Circumstances in which required

The decision whether lysimeter studies are to be carried out, as an experimental outdoor study in the framework of a tiered leaching assessment scheme shall take into account the results of degradation and other mobility studies and the predicted environmental concentrations in groundwater (PEC_{GW}). The type and conditions of the study to be performed shall be discussed with the national competent authorities.

Test conditions

Studies shall cover the realistic worst case situation, and the duration necessary for observation of potential leaching, taking into account the soil type, climatic conditions, the application rate and the frequency and period of application.

Water percolating from soil columns shall be analysed at suitable intervals, while residues in plant material shall be determined at harvest. Residues in the soil profile in at least five layers shall be determined on termination of experimental work. Intermediate sampling shall be avoided, since removal of plants (except for harvesting in accordance with normal agricultural practice) and soil influence the leaching process.

Precipitation, soil and air temperatures shall be recorded at regular intervals, at least on a weekly base.

The depth of the lysimeters shall be at least 100 cm. The soil cores shall be undisturbed. Soil temperatures shall be similar to those pertaining in the field. Where necessary, supplementary irrigation shall be provided to ensure optimal plant growth and to ensure that the quantity of percolation water is similar to that in the regions for which authorisation is sought. When during the study the soil has to be disturbed for agricultural reasons it shall not be disturbed deeper than 25 cm.

7.1.4.3. Field leaching studies

Field leaching studies shall be performed, where necessary, to provide information on:

— the mobility in soil,

— the potential for leaching to ground water,

— the potential distribution in soil.

Circumstances in which required

The decision whether field leaching studies are to be carried out, as an experimental outdoor study in the framework of a tiered leaching assessment scheme shall take into account the results of degradation and other mobility studies and the predicted environmental concentrations in groundwater (PEC_{GW}).

Test conditions

Studies shall cover the realistic worst case situation, taking into account the soil type, climatic conditions, the application rate and the frequency and period of application.

Water shall be analysed at suitable intervals. Residues in the soil profile in at least five layers shall be determined on termination of experimental work. Intermediate sampling of plant and soil material shall be avoided since removal of plants and soil influence the leaching process.

Precipitation, soil and air temperatures shall be recorded at regular intervals (at least on a weekly base).

Information on the groundwater table in the experimental fields shall be submitted. Depending on the experi- mental design, a detailed hydrological characterisation of the test field shall be carried out. If soil cracking is observed during the study this shall be fully described.

Attention shall be given to the number and the location of water collection devices. The placement of these devices in the soil shall not result in preferential flow paths.

7.2. Fate and behaviour in water and sediment

The information provided, taken together with that provided for one or more final product containing the active substance, and other relevant information, shall be sufficient to establish or permit estimation of:

(a) persistence in water systems (bottom sediment and water, including suspended particles);

(b) the extent to which water and sediment organisms are at risk;

(c) potential for contamination of surface water and groundwater.

7.2.1. Route and rate of degradation in aquatic systems (chemical and photochemical degradation)

The data and information provided, together with other relevant data and information, shall be sufficient to:

(a) identify the relative importance of the types of processes involved (balance between chemical and biological degradation);

(b) where possible, identify the individual components present;

(c) establish the relative proportions of the components present and their distribution as between water, including suspended particles, and sediment; and

(d) permit the residue of concern to which non-target species are or may be exposed, to be defined.

7.2.1.1. Hydrolytic degradation

Circumstances in which required

The hydrolysis rate of purified active substances shall be determined and reported at 20 °C or 25 °C. Studies on hydrolytic degradation shall also be performed for degradation and reaction products which account at anytime for more than 10 % of the amount of active substance added in the hydrolysis study, unless sufficient information on their degradation is available from the test performed with the active substance. No additional hydrolysis information on degradates shall be required if they are considered to be stable in water.

Test conditions

The hydrolysis rate for pH 4, 7 and 9 under sterile conditions in the absence of light shall be determined and reported at 20 °C or 25 °C. For active substances that are stable or have a low rate of hydrolysis at 20-25 °C, the rate shall be determined at 50 °C, or another temperature above 50 °C. If degradation is observed at 50 °C or above, the degradation rate at least three other temperatures shall be determined and an Arrhenius plot shall be constructed to permit an estimate to be made of hydrolysis rate at 20 °C and 25 °C. The identity of hydrolysis products formed and the rate constants observed, shall be reported. The estimated DegT50 values shall be reported for 20 °C or 25 °C.

Direct photochemical degradation

Circumstances in which required

For compounds with a molar (decadic) absorption coefficient (ε) > 10 L × mol^{-1} × cm^{-1} at a wavelength (λ) ≥ 295 nm direct phototransformation of purified active substances shall be determined and reported unless the applicant shows that contamination of surface water will not occur.

Studies on direct photochemical degradation shall also be performed for metabolites, breakdown and reaction products which account at any time for more than 10 % of the amount of active substance added in the photolysis study, unless sufficient information on their degradation is available from the test performed with the active substance.

No additional photolysis information on degradates shall be required if they are considered to be stable under photolytic conditions.

Test conditions

The direct phototransformation in purified, (for example distilled) buffered water using artificial light under sterile conditions, if necessary using a solubiliser, shall be determined and reported. In the first theoretical step a maximum possible photolysis rate shall be estimated based on the molar extinction coefficient of the active substance. If photolysis is considered to be a potentially significant degradation pathway, photolysis experiments for range finding shall be carried out (tier 2). Determination of quantum yield and direct photolysis route/rate (tiers 3 and 4) shall be carried out for active substances where tier 2 indicates significant photolysis. The identity of breakdown products formed which exceed 10 % of the applied test substance at any time during the study, a mass balance to account for at least 90 % of the applied radioactivity, as well as photochemical half-life (DT50) shall be reported.

7.2.1.2. Indirect photochemical degradation

Circumstances in which required

Studies on indirect photochemical degradation may be submitted where there are indications from other available data that route and rate of degradation in the water phase can be significantly influenced by indirect photodegradation.

Test conditions

Studies shall be performed in an aqueous system containing organic (humic substances) and

inorganic (salts) compounds in a composition that is typical for natural surface waters.

7.2.2. Route and rate of biological degradation in aquatic systems

7.2.2.1. 'Ready biodegradability'

Circumstances in which required

The 'ready biodegradability' test shall be performed. If no such test is provided, the active substance shall by default be considered not 'readily biodegradable'.

7.2.2.2. Aerobic mineralisation in surface water

The data and information provided, together with other relevant data and information, shall be sufficient to:

(a) identify individual components present, which at any time account for more than 10 % of the amount of active substance added, including, where possible, non-extractable residues;

(b) identify individual components present, which account for more than 5 % of the amount of active substance added in at least two sequential measurements, where possible;

(c) identify individual components (> 5 %) for which at the end of the study the maximum of formation is not yet reached, where possible;

(d) identify or characterise, where possible, other individual components;

(e) establish, where relevant, the relative proportions of the components (mass balance); and

(f) permit, where relevant, the sediment residue of concern and to which non-target species are or may be exposed, to be defined.

Circumstances in which required

Studies on aerobic mineralisation in surface water shall be provided unless the applicant shows that contamination of open water (freshwater, estuarine and marine) will not occur.

Test conditions

The rate of degradation and the pathway or pathways shall be reported either for a 'pelagic' test system or for a 'suspended sediment' system. Where relevant, additional test systems, which differ with respect to organic carbon content, texture or pH shall be used.

Results obtained shall be presented in the form of schematic drawings showing the pathways involved, and in the form of balance sheets which show the distribution of radio-label in water and, where relevant, sediment as a function of time, as between:

(a) active substance;

(b) CO_2;

(c) volatile compounds other than CO_2; and

(d) individual identified transformation products.

The duration of the study shall not exceed 60 days unless the semi-continuous procedure with periodical renewal of the test suspension is applied. However, the period for the batch test may be extended to a maximum of 90 days, if the degradation of the test substance has

started within the first 60 days.

7.2.2.3. Water/sediment study

The information provided, together with other relevant information, shall be sufficient to:

(a) identify individual components present which at any time account for more than 10 % of the amount of active substance added, including, where possible, non-extractable residues;

(b) identify individual components present which account for more than 5 % of the amount of active substance added in at least two sequential measurements, where possible;

(c) identify individual components (> 5 %) for which at the end of the study the maximum of formation is not yet reached, where possible;

(d) identify or characterise, where possible, also other individual components present;

(e) establish the relative proportions of the components (mass balance); and

(f) define the sediment residue of concern, to which non-target species are or may be exposed.

Where a reference is made to non-extractable residues these shall be defined as chemical species originating from active substances used in accordance with good agricultural practice that cannot be extracted by methods which do not significantly change the chemical nature of these residues or the nature of the sediment matrix. These non-extractable residues are not considered to include fragments through metabolic pathways leading to natural products.

Circumstances in which required

The water/sediment study shall be reported unless the applicant shows that contamination of surface water will not occur.

Test conditions

The degradation pathway or pathways shall be reported for two water/sediment systems. The two sediments selected shall differ with respect to organic carbon content and texture, and where relevant, with respect to pH.

Results obtained shall be presented in the form of schematic drawings showing the pathways involved, and in the form of balance sheets which show the distribution of radio-label in water and sediment as a function of time, as between:

(a) active substance;

(b) CO_2;

(c) volatile compounds other than CO_2;

(d) individual identified transformation products;

(e) extractable substances not identified; and

(f) non-extractable residues in sediment.

The duration of the study shall be at least 100 days. It shall be longer where this is necessary to establish the degradation pathway and water/sediment distribution pattern of the active substance and its metabolites, breakdown and reaction products. If more than 90 % of the active substance is degraded before the period of 100 days expires, the test duration may be shorter.

The degradation pattern of potentially relevant metabolites occurring within the water/sediment study shall be established either by extension of the study for the active substance, or by conducting a separate study for potentially relevant metabolites.

7.3. Fate and behaviour in air

7.3.1. Route and rate of degradation in air

The vapour pressure of purified active substance, as provided under point 2.2, shall be reported. An estimate of the half-life in the upper atmosphere of the active substance and any volatile metabolites, breakdown and reaction products, formed in soil or natural water systems, shall be calculated and reported.

Estimates of active substance upper atmospheric half-lives, based on monitoring data shall also be calculated, when monitoring data that enable this to be done, are available.

7.3.2. Transport via air

The type and conditions of the study to be performed shall be discussed with the national competent auth- orities.

Circumstances in which required

If the trigger for volatilisation, Vp = 10^{-5} Pa (plant) or 10^{-4} Pa (soil) at a temperature of 20 °C, is exceeded and (drift) mitigation measures are required, data from confined experiments may be reported.

If needed, experiments to determine deposition following volatilisation may be provided.

The national competent authorities shall be consulted to decide whether this information is necessary.

7.3.3. Local and global effects

For substances that are applied in high amounts, the following effects shall be considered:

— global warming potential (GWP);

— ozone depleting potential (OPD);

— photochemical ozone creation potential (POCP);

— accumulation in the troposphere;

— acidification potential (AP);

— eutrophication potential (EP).

7.4. Definition of the residue

7.4.1. Definition of the residue for risk assessment

The residue definition relevant for risk assessment for each compartment shall be defined to include all components (active substance, metabolites, breakdown and reaction products) that were identified in accordance with the criteria referred to in this Section.

The chemical composition of residues occurring in soil, groundwater, surface water (freshwater, estuarine and marine), sediment and air, resulting from use, or proposed use, of a VPP containing the active substance, shall be taken into account.

7.4.2. Definition of the residue for monitoring

Considering the results of toxicological and ecotoxicological testing, the residue for monitoring shall be defined to include those components from the definition of the residue for risk assessment, which are considered relevant when assessing the results in those tests.

7.5. Monitoring data

Available monitoring data concerning fate and behaviour of the active substance and relevant metabolites, breakdown and reaction products in soil, groundwater, surface water, sediment and air shall be reported.

PART A: SECTION 8

ECOTOXICOLOGICAL STUDIES

Introduction

1. All available biological data and information which is relevant to the assessment of the ecotoxicological profile of the active substance shall be reported. This shall include all potentially adverse effects found during routine ecotoxicological investigations. Where required by the national competent authorities, additional studies, necessary to investigate the probable mechanisms involved and to assess the significance of these effects, shall be carried out and reported on.

2. The ecotoxicological assessment shall be based on the risk that the proposed active substance used in a finished product poses to non-target organisms. In carrying out a risk assessment, toxicity shall be compared with exposure. The general term for the output from such a comparison is 'risk quotient' or RQ. It shall be noted that RQ can be expressed in several ways, for example, toxicity:exposure ratio (TER) and as a hazard quotient (HQ). The applicant shall take into account the information from Sections 2, 5, 6, 7 and 8.

3. It may be necessary to conduct separate studies for metabolites, breakdown or reaction products derived from the active substance where non-target organisms may be exposed and where their effects cannot be evaluated by the available results relating to the active substance. Before such studies are performed, the applicant shall take into account the information from Sections 5, 6 and 7.

   Studies undertaken shall permit characterisation of metabolites, breakdown or reaction products as being significant or not, and reflect the nature and extent of the effects judged likely to arise.

4. In the case of certain study types, the use of a representative finished product instead of the active substance as manufactured may be more appropriate, for example testing of non-target arthropods, bees, earthworm reproduction, soil micro-flora and non-target terrestrial plants. In the case of certain finished product types (for example encapsulated suspension) testing with the finished product is more appropriate to testing with active substance when these organisms will be exposed to the finished product itself. For finished products where the active substance is always intended to be used together with a safener and/or synergist and/or in conjunction with other active substances, finished products containing these additional substances shall be used.

5. The potential impact of the active substance on biodiversity and the ecosystem, including potential indirect effects via alteration of the food web, shall be considered.

6. For those guidelines which allow for the study to be designed to determine an effective concentration (EC_X), the study shall be conducted to determine an EC_{10}, EC_{20} and EC_{50}, when required, along with corresponding 95 % confidence intervals. If an EC_X approach is used, a no observed effect concentration (NOEC) shall still be determined.

   Existing acceptable studies that have been designed to generate a NOEC shall not be repeated. An assessment of the statistical power of the NOEC derived from those studies shall be carried out.

7. All of the aquatic toxicity data shall be used when developing a proposal for environmental quality standards (Annual Average EQS, AA-EQS; Maximum Acceptable Concentration EQS, MAC-EQS).

8. In order to facilitate the assessment of the significance of test results obtained, including the estimation of intrinsic toxicity and the factors affecting toxicity, the same strain (or recorded origin) of each relevant species shall, where possible, be used in the various toxicity tests specified.

9. Higher tier studies shall be designed and data analysed using suitable statistical methods. Full details of the statistical methods shall be reported. Where appropriate and necessary, higher tier studies shall be supported by chemical analysis to verify exposure has occurred at an appropriate level.

10. Pending the validation and adoption of new studies and of a new risk assessment scheme, existing protocols shall be used to address the acute and chronic risk to bees, including those on colony survival and devel- opment, and the identification and measurement of relevant sub-lethal effects in the risk assessment.

8.1. Effects on birds and other terrestrial vertebrates

For all avian and mammalian feeding studies, average achieved dose shall be reported, including where possible the dose in mg substance/kg body weight. Where dosing via the diet is utilised, the active substance shall be distributed uniformly in the diet.

8.1.1. Effects on birds

8.1.1.1. Acute oral toxicity to birds

The acute oral toxicity of the active substance to birds shall be determined.

Circumstances in which required

The effects of the active substance on birds shall be investigated except where the substance is included in final product used where birds will experience neither direct nor secondary exposure.

Test Conditions

A study shall be provided establishing the acute oral toxicity (LD_{50}) of the active substance. Where available, the study shall be performed with a quail species (Japanese quail (*Coturnix coturnix japonica*) or Bobwhite quail (*Colinus virginianus*)), since regurgitation is rare in these species. The study shall provide, where possible, LD_{50} values. The lethal threshold dose, time courses of response and recovery, the LD_{10} and LD_{20} shall be reported together with the no observed effect level (NOEL) and gross pathological findings. Where LD_{10} and LD_{20} cannot be estimated, an explanation shall be provided. Study design shall be optimised for the achievement of an accurate LD_{50}.

The highest dose used in tests shall not exceed 2 000 mg substance/kg body weight, however, depending on the expected exposure levels in the field following the intended use of the compound, higher doses may be required.

8.1.1.2. Short-term dietary toxicity to birds

A study shall be provided establishing the short-term dietary toxicity. LC_{50} values, lowest lethal concentration (LLC), where possible, NOEC values, time courses of response and recovery and pathological findings shall be reported in such study. LC_{50} and NOEC values shall be converted to daily dietary dose (LD_{50}) expressed in mg substance/kg bw/day and NOEL expressed in mg substance/kg bw/day.

Circumstances in which required

A study on the dietary (five-day) toxicity of the active substance to birds shall only be required where the mode of action or results from mammalian studies indicate a potential for the dietary LD_{50} measured by the short- term dietary toxicity study to be lower than the LD_{50} based on an acute oral study. The short-term dietary toxicity test shall not be conducted for any other purpose than to determine intrinsic toxicity through dietary exposure, unless a justification of the need

to do so is supplied.

Test conditions

The test species shall be the same as tested under point 8.1.1.1.

8.1.1.3. Sub-chronic and reproductive toxicity to birds

A study shall be provided establishing the sub-chronic and reproductive toxicity of the substance to birds. The EC_{10} and EC_{20} shall be reported. Where they cannot be estimated, an explanation shall be provided together with the NOEC expressed in mg substance/kg bw/day.

Circumstances in which required

The sub-chronic and reproductive toxicity of the active substance to birds shall be investigated, unless the applicant shows that exposure of adults, or exposure of nest sites during the breeding season is unlikely to occur. Such a justification shall be supported by information showing that no exposure or delayed effects will occur during the breeding season.

Test conditions

The study shall be conducted on the same species as tested under point 8.1.1.1.

8.1.2. Effects on terrestrial vertebrates other than birds

The following information shall be derived from the mammalian toxicological assessment based on the studies referred to in Section 5.

8.1.2.1. Acute oral toxicity to mammals

The acute oral toxicity of the active substance to mammals shall be determined and the LD_{50} expressed mg substance/kg bw/day.

Circumstances in which required

The effects of the active substance on mammals shall be investigated except when the substance is included in final product used where mammals will experience neither direct nor secondary exposure.

8.1.2.2. Long-term and reproductive toxicity to mammals

Circumstances in which required

The reproductive toxicity of the active substance to mammals shall be investigated, unless a justification is provided by the applicant showing that exposure of adults, during the breeding season is unlikely to occur. Such a justification shall be supported by information showing that no exposure or delayed effects will occur during the breeding season.

The most sensitive ecotoxicologically relevant mammalian long-term toxicological endpoint (NOAEL) expressed as mg substance/kg bw/day shall be reported. The EC_{10} and EC_{20} shall be reported together with the NOEC expressed in mg substance/kg bw/day. Where EC_{10} and EC_{20} cannot be estimated an explanation shall be provided.

8.1.3. Active substance bioconcentration in prey of birds and mammals

For active substances with a log Pow > 3, an assessment of the risk posed by bioconcentration of the substance in the prey of birds and mammals shall be provided.

8.1.4. Effects on terrestrial vertebrate wildlife (birds, mammals, reptiles and amphibians)

Available and relevant data, including data from the open literature for the active substance

of concern, regarding the potential effects to birds, mammals, reptiles and amphibians (see point 8.2.3) shall be presented and taken into account in the risk assessment.

8.1.5. Endocrine disrupting properties

Consideration shall be given to whether the active substance is a potential endocrine disruptor according to Union or internationally agreed guidelines. This may be done in consulting the mammalian toxicology section (see Section 5). In addition, other available information on toxicity profile and mode of action shall be taken into account. If as a result of this assessment, the active substance is identified as a potential endocrine disruptor, the type and conditions of the study to be performed shall be discussed with the national competent authorities.

8.2. Effects on aquatic organisms

Reports of the tests referred to in points 8.2.1, 8.2.4 and 8.2.6 shall be submitted for every active substance and supported with analytical data on concentrations of the substance in the test media.

When aquatic toxicity studies are conducted with a poorly soluble substance, limit concentrations lower than 100 mg substance/L may be acceptable, however precipitation of the substance in the test medium shall be avoided and a solubiliser, auxiliary solvent or dispersing agent shall be used when appropriate. Testing using the VPP may be required by the national competent authorities if no biological effects occur at the solubility limit of the active substance.

Toxicity endpoints (such as LC_{50}, EC_{10}, EC_{20}, EC_{50} and NOEC) shall be calculated on the basis of nominal or mean/initial measured concentrations.

8.2.1. Acute toxicity to fish

A study shall be provided on the acute toxicity to fish (LC_{50}) and details of observed effects.

Circumstances in which required

A test on rainbow trout (*Oncorhynchus mykiss*) shall be carried out.

Test conditions

The acute toxicity of the active substance to fish shall be determined. In order to minimise fish testing, a threshold approach to acute toxicity testing on fish shall be considered. An acute toxicity fish limit test shall be conducted at 100 mg substance/L or at an appropriate concentration selected from aquatic endpoints (points 8.2.4, 8.2.6 or 8.2.7) following consideration of the threshold exposure. When mortality is detected in the fish limit test an acute fish dose-response toxicity study shall be required to determine an LC_{50} for use in the risk assessment conducted in accordance with the relevant risk quotient analysis (see point 2 of the introduction of this Section).

8.2.2. Long-term and chronic toxicity to fish

Circumstances in which required

A long-term or chronic toxicity study on fish shall be provided for all active substances where exposure of surface water is likely and the substance is deemed to be stable in water, that is to say there is less than 90 % loss of the original substance over 24 hours via hydrolysis (see point 7.2.1.1). A fish early life stage study shall be provided in these circumstances. However, if a fish full life cycle study is provided an early life stage study shall not be required.

8.2.2.1. Fish early life stage toxicity test

A fish early life stage toxicity test shall determine effects on development, growth and behaviour, and details of observed effects on fish early life stages. The EC_{10} and EC_{20} shall be reported together with the NOEC. Where EC_{10} and EC_{20} cannot be estimated, an explanation shall be provided.

8.2.2.2. Fish full life cycle test

A fish full life cycle test shall provide information on the effects on reproduction of the parental and the viability of the filial generation. The EC_{10} and EC_{20} shall be reported together with the NOEC.

For active substances that are not considered as potential endocrine disruptors, a fish full life cycle test may be required depending upon the persistence and bioaccumulative potential of the substance.

For active substances that fulfil the screening criteria on either of the fish screening assays, or for which there are other indications of endocrine disruption (see point 8.2.3), appropriate additional endpoints shall be included in the test and discussed with the national competent authorities.

Test conditions

Studies shall be designed to reflect concerns identified through lower tier testing, mammalian and bird toxicology studies and other information. The exposure regime shall be selected accordingly, taking account of the rates of application proposed.

8.2.2.3. Bioconcentration in fish

The test on bioconcentration in fish shall provide the steady-state bioconcentration factors, uptake rate constants and depuration rate constants, incomplete excretion, metabolites formed in fish and, if available, information on organ-specific accumulation.

All data shall be provided with confidence limits for each test substance. Bioconcentration factors shall be expressed as a function of both total wet weight and of the lipid content of the fish.

Data provided under point 6.2.5 shall be considered, where relevant, in addressing this point.

Circumstances in which required

The bioconcentration of the substance, shall be assessed where:

— the log Pow is greater than 3 (see point 2.7) or there are other indications of bioconcentration, and

— the substance is considered stable, that is to say there is less than 90 % loss of the original substance over 24 hours via hydrolysis (see point 7.2.1.1).

8.2.3. Endocrine disrupting properties

Consideration shall be given to whether the active substance is a potential endocrine disruptor in

aquatic non- target organisms according to Union or internationally agreed guidelines. In addition, other available information on toxicity profile and mode of action shall be taken into account. If as a result of this assessment, the active substance is identified as a potential endocrine disruptor, the type and conditions of the studies to be performed shall be discussed with the national competent authorities.

8.2.4. *Long-term and chronic toxicity to aquatic invertebrates*

Circumstances in which required

A long-term or chronic toxicity study on aquatic invertebrates shall be provided for all active substances where exposure of surface water is likely and the substance is deemed to be stable in water, that is to say there is less than 90 % loss of the original substance over 24 hours via hydrolysis (see point 7.2.1.1).

A chronic toxicity study shall be submitted on one aquatic invertebrate species. If acute toxicity tests have been conducted on two aquatic invertebrate species the acute endpoints shall be taken into account (see point 8.2.4) in order to determine the appropriate species to be tested in the chronic toxicity study.

If the active substance is an insect growth regulator, an additional study on chronic toxicity shall be carried out using relevant non-crustacean species such as *Chironomus* spp.

8.2.4.1. Reproductive and development toxicity to *Daphnia magna*

The aim of the test on reproductive and development toxicity to *Daphnia magna* shall be to measure adverse effects such as immobilisation and loss of reproductive capacity and to provide details of observed effects. The EC_{10}, and EC_{20} shall be reported together with the NOEC. Where EC_{10} and EC_{20} cannot be estimated, an explanation shall be provided.

Reproductive and development toxicity to an additional aquatic invertebrate species

The test on reproductive and development toxicity to an additional aquatic invertebrate species shall measure adverse effects such as immobilisation and loss of reproductive capacity and provide details of observed effects. The EC_{10}, and EC_{20} shall be reported together with the NOEC. Where EC_{10} and EC_{20} cannot be estimated, an explanation shall be provided.

8.2.4.2. Development and emergence in *Chironomus riparius*

The active substance shall be applied to the water overlying sediment and effects on survival and development of *Chironomus riparius*, including effects on emergence of adults, shall be measured to provide endpoints for those substances considered to interfere with insect moulting hormones or that have other effects on insect growth and development. The EC_{10} and EC_{20} shall be reported together with the NOEC.

Test conditions

Concentrations of active substance in the overlying water and the sediment shall be measured to establish an EC_{10}, EC_{20} and a NOEC. The active substance shall be measured often enough to allow the calculation of test endpoints based on nominal as well as time-weighted average concentrations.

8.2.4.3. Sediment dwelling organisms

When accumulation of an active substance in aquatic sediment is indicated or predicted by environmental fate studies, the impact on a sediment-dwelling organism shall be assessed. The chronic risk to *Chironomus riparius* or *Lumbriculus* spp. shall be determined. An appropriate alternative test species may be used where a recognised guideline is available. The active substance shall be applied to either the water or the sediment phase of a water/sediment system and the test shall take account of the major route of exposure. The key endpoint from the study shall be presented in terms of mg substance/kg dry sediment and mg substance/L water and the EC_{10} and EC_{20} shall be reported together with the NOEC.

Test conditions

Concentrations of active substance in the overlying water and the sediment shall be measured to establish an EC_{10}, EC_{20} and a NOEC.

8.2.5. Further testing on aquatic organisms

Further studies on aquatic organisms may be conducted to refine the identified risk and shall provide sufficient information and data to evaluate potential impact on aquatic organisms under field conditions.

Studies undertaken may take the form of additional species testing, modified exposure testing, microcosm or mesocosm studies.

8.3. Effect on arthropods

8.3.1. Effects on bees

Effects on bees shall be assessed and the risk evaluated, including the risk deriving from residues of the active substance or its metabolites in nectar, pollen and water, including guttation. Reports of the tests referred to in points 8.3.1.1, 8.3.1.2 and 8.3.1.3 shall be submitted, except where finished product containing the active substance are for exclusive use in situations where bees are not likely to be exposed.

Where bees are likely to be exposed, testing by both acute (oral and contact) and chronic toxicity, including sub-lethal effects, shall be conducted.

Where exposure of bees to residues in nectar, pollen or water resulting from systemic properties of the active substance may occur and where the acute oral toxicity is < 100 µg/bee or a considerable toxicity for larvae occurs, residues concentrations in these matrices shall be provided and the risk assessment shall be based on a comparison of the relevant endpoint with those residue concentrations. If this comparison indicates that an exposure to toxic levels cannot be excluded, effects shall be investigated with higher tier tests.

8.3.1.1. Acute toxicity to bees

Where bees are likely to be exposed, testing for acute oral and contact toxicity shall be performed.

8.3.1.1.1. Acute oral toxicity

A test for acute oral toxicity shall be provided establishing the acute LD_{50} values together with the NOEC. Sub-lethal effects, if observed, shall be reported.

Test conditions

The test shall be conducted with the active substance. Results shall be presented in terms of µg active substance/bee.

8.3.1.1.2. Acute contact toxicity

A test for acute contact toxicity shall be provided establishing the acute LD_{50} values together with the NOEC. Sub-lethal effects, if observed, shall be reported.

Test conditions

The test shall be conducted with the active substance. Results shall be presented in terms of µg active substance/bee.

8.3.1.2. Chronic toxicity to bees

A test for chronic toxicity to bees shall be provided establishing the chronic oral EC_{10}, EC_{20}, EC_{50} together with the NOEC. Where the chronic oral EC_{10}, EC_{20}, EC_{50} cannot be estimated, an explanation shall be provided. Sub-lethal effects, if observed, shall be reported.

Circumstances in which required

The test shall be carried out where bees are likely to be exposed.

Test conditions

The test shall be conducted with the active substance. Results shall be presented in terms of µg active substance/bee.

8.3.1.3. Effects on honeybee development and other honeybee life stages

A bee brood study shall be conducted to determine effects on honeybee development and brood activity. The bee brood study shall provide sufficient information to evaluate possible risks from the active substance on honeybee larvae.

The test shall provide the EC_{10}, EC_{20} and EC_{50} for adult bees, where possible, and larvae together with the NOEC. Where EC_{10}, EC_{20}, EC_{50} cannot be estimated, an explanation shall be provided. Sub-lethal effects, if observed, shall be reported.

Circumstances in which required

The test shall be carried out for active substances for which sub-lethal effects on growth or development cannot be excluded, unless the applicant shows that it is not possible that honeybee brood will be exposed to the active substance.

8.3.1.4. Sub-lethal effects

Tests investigating sub-lethal effects, such as behavioural and reproductive effects, on bees and, where applicable, on colonies may be required.

8.3.2. Effects on non-target arthropods other than bees

Circumstances in which required

Effects on non-target terrestrial arthropods shall be investigated for all active substances except

where finished product containing the active substance are for exclusive use in situations where non-target arthropods are not exposed.

Initial testing shall be performed using glass plates and mortality (and reproduction effects if assessed) shall be reported. Testing shall determine a rate-response relationship and LR_{50} (1), ER_{50} (2) and NOEC endpoints shall be reported for assessment of the risk to these species in accordance with the relevant risk quotient analysis. If adverse effects can be clearly predicted from these studies then testing using higher tier studies may be required.

With active substances suspected of having a special mode of action (such as insect growth regulators, insect feeding inhibitors) additional tests involving sensitive life stages, special routes of uptake or other modifications, may be required by the national competent authorities. The rationale for the choice of test species used shall be provided.

8.4. Effects on non-target soil meso- and macrofauna

8.4.1. Earthworm — sub-lethal effects

A test shall provide information on the effects on growth, reproduction and behaviour of the earthworm.

Circumstances in which required

Sub-lethal effects on earthworms shall be investigated where the active substance can contaminate soil.

Test conditions

Testing shall determine a dose-response relationship and the EC_{10}, EC_{20} and NOEC shall enable the risk assessment to be conducted in accordance with the appropriate risk quotient analysis, taking into account likely exposure, the organic carbon content (f_{OC}) of the test medium and the lipophilic properties (K_{OW}) of the test substance. The test substance shall be incorporated into the soil to obtain a homogenous soil concentration. Testing with soil metabolites may be avoided if there is analytical evidence to indicate that the metabolite is present at an adequate concentration and duration in the study conducted with the parent active substance.

8.4.2. Effects on non-target soil meso- and macrofauna (other than earthworms)

Circumstances in which required

Effects on soil organisms, other than earthworms, shall be investigated for all test substances, except in situations where soil organisms are not exposed.

8.4.2.1. Species level testing

A test shall provide sufficient information to perform an assessment of the toxicity of the active substance to the soil invertebrate indicator species *Folsomia candida* and *Hypoaspis aculeifer*.

Test conditions

Testing shall determine a dose-response relationship and the EC_{10}, EC_{20} and NOEC shall enable the risk assessment to be conducted in accordance with the appropriate risk quotient analysis, taking into account likely exposure, the organic carbon content (f_{OC}) of the test medium and the lipophilic properties (K_{OW}) of the test substance. The test substance shall be

incorporated into the soil to obtain a homogenous soil concen- tration. Testing with soil metabolites may be avoided if there is analytical evidence to indicate that the metabolite is present at an adequate concentration and duration in the study conducted with the parent active substance.

8.5. Effects on soil nitrogen transformation

A test shall provide sufficient data to evaluate the impact of active substances on soil microbial activity, in terms of nitrogen transformation.

Circumstances in which required

The test shall be carried out where final product containing the active substance are applied to soil or can contaminate soil under practical conditions of use. In the case of active substances intended for use in final product for soil sterilisation, the studies shall be designed to measure rates of recovery following treatment.

Test conditions

Soils used shall be freshly sampled agricultural soils. The sites from which soil is taken shall not have been treated during the previous two years with any substance that could substantially alter the diversity and levels of microbial populations present, other than in a transitory manner.

8.6. Effects on other terrestrial organisms (flora and fauna)

Any available data on the effects of the product on other terrestrial organisms shall be submitted.

8.7. Effects on biological methods for sewage treatment

A test shall provide an indication as to the potential of the active substance on biological sewage treatment systems.

Circumstances in which required

Effects on biological methods for sewage treatment shall be reported where the use of VPPs containing the active substance can give rise to adverse effects on sewage treatment plants.

8.8. Monitoring data

Available monitoring data concerning adverse effects of the active substance to non-target organisms shall be reported.

PART A: *SECTION 9*

REFERENCES

References from the scientific peer reviewed open literature on the active substance, metabolites and breakdown or reaction products and VPPs containing the active substance shall be submitted.

PART A: SECTION 10

CLASSIFICATION AND LABELLING

Proposals for the classification and labelling/Artwork of the packaging materials of the active substance in shall be submitted according to the guideline for labelling of a veterinary pesticide product and justified, including:

— pictograms,

— signal words,

— hazard statements, and

— precautionary statements.

PART B: REGISTRATION OF FINISHED PESTICIDE PRODUCT (FPP)

TECHNICAL INFORMATION REQUIRED

INTRODUCTION

The information submitted shall meet the following requirements;

1.1 The information shall be sufficient to evaluate the foreseeable risks, whether immediate or delayed, which the FPP may entail for humans, including vulnerable groups, animals and the environment and contain at least the information and results of the studies referred to in this guidelines.

1.2 Any information on potentially harmful effects of the FPP, its metabolites and impurities on human and animal health or on groundwater shall be included.

1.3 Any information on potentially unacceptable effects of the active substance, its metabolites and impurities on the environment, on plants and plant products shall be included.

1.4 The information shall include all relevant data from the scientific peer reviewed open literature on the FPP, metabolites and breakdown or reaction products and finished products containing the active substance and dealing with side-effects on health, the environment and non-target species. A summary of this data shall be provided.

1.5 The information shall include a full and unbiased report of the studies conducted as well as a full description of them. Such information shall not be required, where one of the following conditions is fulfilled:

c) It is not necessary owing to the nature of the product or its proposed uses, or it is not scientifically necessary;
d) It is technically not possible to supply.
In such a case a justification shall be provided.

1.6 The simultaneous use of the active substance as a biocide shall be reported.

1.7 Where relevant, the information shall be generated using test methods which are referred to in these guidelines.

1.8 The information shall include a full description of the test methods used.

1.9 The information shall include a list of endpoints for the FPP.

1.10 The information provided for the FPP and that provided for the active substance, shall be sufficient to:

(a) decide whether, or not, the product is to be authorised;
(b) specify conditions or restrictions to be associated with any authorisation;

b) permit an evaluation of short and long-term risks for non-target species, populations, communities and processes;

(c) identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of poisoning in humans;

(d) permit a risk assessment of acute and chronic consumer exposure, including, where relevant, a cumulative risk assessment deriving from exposure to more than one active substance;

(e) permit an estimation of acute and chronic exposure to operators, workers, residents and bystanders including, where relevant, the cumulative exposure to more than one active substance;

(f) permit an evaluation to be made as to the nature and extent of the risks for humans, animals

(species normally fed and kept by humans or food producing animals) and of the risks for other non-target vertebrate species;

(g) predict the distribution, fate, and behaviour in the environment, as well as the time courses involved;

(h) identify non-target species and populations for which hazards arise because of potential exposure;

(i) permit an assessment of the impact of the product on non target species;

(j) identify measures necessary to minimise contamination of the environment and impact on non-target species;

(k) classify the product as to hazard.

1.11 Where relevant, tests shall be designed and data analysed using appropriate statistical methods.

1.12 Exposure calculations shall refer to scientific methods accepted by VMD, when available. Additional methods, when used, shall be justified.

1.13 For each section of the data requirements, a summary of all data, information and evaluation made shall be submitted.

2. The requirements set out in this guidelines shall represent the minimum data to be submitted. Additional requirements may be necessary in specific circumstances, that is to say specific scenarios, patterns of use other than those taken into account for approval. Careful attention shall be given to environmental, climatic and agronomic conditions when tests are set up and approved by the competent authorities.

3. Good laboratory practice (GLP)

3.1 Where testing is done to obtain data on the properties or safety with respect to human or animal health or the environment, these will be done in accordance with GLP

3.2 For analytical test, if shall be done in accordance with the GLP requirements and shall be conducted by laboratories accredited for the relevant method.

4. Test material

4.1 A detailed description (specification) of the material used shall be provided. Where tests are done using the FPP, the material used shall comply with the specification that will be used in the manufacture of the finished product to be authorised, except where radio-labelled material or the purified active substance is used.

4.2 Where studies are conducted using an active substance produced in the laboratory or in a pilot plant production system, the studies shall be repeated using the FPP as manufactured, unless the applicant shows that the test material used is essentially the same, for the purposes of toxicological, ecotoxicological, environmental and residue testing and assessment. In cases of uncertainty, bridging studies shall be submitted to serve as a basis for a decision as to the possible need for repetition of the studies.

4.3 Where studies are conducted using an FPP of different purity or which contains different impurities or different levels of impurities to the technical specification or where the active substance is a mixture of components, the significance of the differences shall be addressed either by data or scientific case. In cases of uncertainty, appropriate studies using the active substance as manufactured for commercial production shall be submitted to serve as a basis for a decision.

4.4 In the case of studies in which dosing extends over a period (for example repeated dose studies), dosing shall be done using a single batch of active substance if stability permits. Whenever a study implies the use of

different doses, the relationship between dose and adverse effect shall be reported.

4.5 Where radio-labelled test material is used, radio-labels shall be positioned at sites (one or more as necessary), to facilitate elucidation of metabolic and transformation pathways and to facilitate investigation of the distribution of the active substance and of its metabolites, reaction and breakdown products.

5. Tests on vertebrate animals

5.1 Where tests on vertebrate animals are undertaken, reduction and refinement methods for *in vivo* testing shall be encouraged to keep the number of animals used in testing to a minimum.

5.2 The principles of replacement, reduction and refinement of the use of animals shall be taken into account in the design of the test methods, in particular when appropriate validated methods become available to replace, reduce or refine animal testing.

5.3 Tests involving the deliberate administration of the active substance or the finished products to humans and non-human primates shall not be performed for the purpose of this guideline.

5.4 For ethical reasons, study designs shall be carefully considered, taking into account the scope for reduction, refinement and replacement of animal tests. For example, by including one or more additional dose groups or time points for blood sampling in one study, it may be possible to avoid the need for another study.

SECTION 1 ***IDENTITY OF THE FPP***

1.1. Applicant

1.2. Producer of the FPP and the active substances

1.3. Trade name or proposed trade name and producer's development code number of the FPP if appropriate

1.4. Detailed quantitative and qualitative information on the composition of the FPP

1.4.1. Composition of the FPP

1.4.2. Information on the active substances

1.4.3. Information on safeners, synergists and co-formulants

1.5. Type and code of the FPP

1.6. Function

SECTION 2 ***PHYSICAL, CHEMICAL AND TECHNICAL PROPERTIES OF THE FPP***

2.1. Appearance

2.2. Explosive and oxidising properties

2.3. Flammability and self-heating

2.4. Acidity/alkalinity and pH value

2.5. Viscosity and surface tension

2.6. Relative density and bulk density

2.7. Storage stability and shelf-life: effects of temperature on technical characteristics of the FPP

2.8. Technical characteristics of the FPP

2.8.1. Wettability

2.8.2. Persistent foaming

2.8.3. Suspensibility, spontaneity of dispersion and dispersion stability

2.8.4. Degree of dissolution and dilution stability

2.8.5. Particle size distribution, dust content, attrition and mechanical stability

2.8.5.1. Particle size distribution

2.8.5.2. Dust content

2.8.5.3. Attrition

2.8.5.4. Hardness and integrity

2.8.6. Emulsifiability, re-emulsifiability, emulsion stability

2.8.7. Flowability, pourability and dustability

2.9. Physical and chemical compatibility with other products including FPPs with which its use is to be authorised

SECTION 3 ***DATA ON APPLICATION/USE***

3.1. Field of use envisaged

3.2. Effects on pests

3.3. Details of intended use

3.4. Application rate and concentration of the active substance

3.5. Method of application

3.6. Number and timing of applications and duration of protection

3.7. Proposed instructions for use

SECTION 4 ***FURTHER INFORMATION ON THE FPP***

4.1. Safety intervals and other precautions to protect humans, animals and the environment

4.2. Recommended methods and precautions

4.3. Emergency measures in the case of an accident

4.4. Packaging, compatibility of the FPP with proposed packaging materials

4.5. Procedures for destruction or decontamination of the FPP and its packaging

4.5.1. Neutralisation procedures

4.5.2. Controlled incineration

SECTION 5 ***ANALYTICAL METHODS***

Introduction

5.1. Methods used for the generation of pre-authorisation data

5.1.1. Methods for the analysis of the FPP

5.1.2. Methods for the determination of residues

5.2. Methods for post-authorisation control and monitoring purposes

SECTION 6 ***EFFICACY DATA***

Introduction

6.1. Preliminary tests

6.2. Testing effectiveness

6.3. Information on the occurrence or possible occurrence of the development of resistance

6.4. Adverse effects on animals

6.4.1. Toxicity to target animals

6.5. Observations on other undesirable or unintended side-effects

6.5.1. Effects on beneficial and other non-target organisms

SECTION 7 ***TOXICOLOGICAL STUDIES***

Introduction

7.1. Acute toxicity

7.1.1. Oral toxicity

7.1.2. Dermal toxicity

7.1.3. Inhalation toxicity

7.1.4. Skin irritation

7.1.5. Eye irritation

7.1.6. Skin sensitisation

7.1.7. Supplementary studies for combinations of FPPs

7.2. Data on exposure

7.2.1. Operator exposure

7.2.1.1. Estimation of operator exposure

7.2.1.2. Measurement of operator exposure

7.2.2. Bystander and resident exposure

7.2.2.1. Estimation of bystander and resident exposure

7.2.2.2. Measurement of bystander and resident exposure

7.2.3. Worker exposure

7.3. Dermal absorption

7.4. Available toxicological data relating to co formulants

SECTION 8 ***RESIDUES IN FOOD AND FEED***

SECTION 9 ***FATE AND BEHAVIOUR IN THE ENVIRONMENT***

Introduction

9.1. Fate and behaviour in soil

9.1.1. Rate of degradation in soil

9.1.1.1. Laboratory studies

9.1.1.2. Field studies

9.1.1.2.1. Soil dissipation studies

9.1.1.2.2. Soil accumulation studies

9.1.2. Mobility in the soil

9.1.2.1. Laboratory studies

9.1.2.2. Lysimeter studies

9.1.2.3. Field leaching studies

9.1.3. Estimation of concentrations in soil

9.2. Fate and behaviour in water and sediment

9.2.1. Aerobic mineralisation in surface water

Water/sediment study

9.2.2. Estimation of concentrations in groundwater

9.2.3. Estimation of concentrations in surface water and sediment

9.3. Fate and behaviour in air

9.3.1. Route and rate of degradation in air and transport via air

9.4. Estimation of concentrations for other routes of exposure

SECTION 10 ***ECOTOXICOLOGICAL STUDIES***

Introduction

10.1. Effects on birds and other terrestrial vertebrates

10.1.1. Effects on birds

10.1.1.1. Acute oral toxicity to birds

10.1.1.2. Higher tier data on birds

10.1.2. Effects on terrestrial vertebrates other than birds

10.1.2.1. Acute oral toxicity to mammals

10.1.2.2. Higher tier data on mammals

10.1.3. Effects on other terrestrial vertebrate wildlife (reptiles and amphibians)

10.2. Effects on aquatic organisms

10.2.1. Acute toxicity to fish, aquatic invertebrates, or effects on aquatic algae and macrophytes

10.2.2. Additional long-term and chronic toxicity studies on fish, aquatic invertebrates and sediment dwelling organisms

10.2.3. Further testing on aquatic organisms

10.3. Effects on arthropods

10.3.1. Effects on bees

10.3.1.1. Acute toxicity to bees10.3.1.1.1. Acute oral toxicity 10.3.1.1.2. Acute contact toxicity

10.3.1.2. Chronic toxicity to bees

10.3.1.3. Effects on honey bee development and other honey bee life stages

10.3.1.4. Sub-lethal effects

10.3.1.5. Cage and tunnel tests

10.3.1.6. Field tests with honeybees

10.4. Effects on non-target soil meso- and macrofauna

10.4.1. Earthworms

10.4.1.1. Earthworms — sub-lethal effects

10.4.1.2. Earthworms — field studies

10.4.2. Effects on non-target soil meso- and macrofauna (other than earthworms)

10.4.2.1. Species level testing

10.4.2.2. Higher tier testing

10.5. Effects on soil nitrogen transformation

10.6. Effects on other terrestrial organisms (flora and fauna)

10.7. Monitoring data

SECTION 11 ***LITERATURE DATA***

SECTION 12 ***CLASSIFICATION AND LABELLING***

PART B: SECTION 1

IDENTITY OF THE FPP

The information provided shall be sufficient to precisely identify the FPP and define it in terms of its specification and nature.

1.1. Applicant

The name and address of the applicant shall be provided, as well as the name, position, telephone, e-mail address and telefax number of a contact point.

1.2. Manufacturer/Producer of the finished product and of the active substances

The name and address of the producer of the FPP and of each active substance in the FPP shall be provided, as well as the name and address of each manufacturing plant in which the FPP and active substance are manufactured. A contact point (name, telephone, e-mail address and telefax number) shall be provided.

1.3. Trade name or proposed trade name

All former and current trade names and proposed trade names and development code numbers of the FPP shall be provided. Where trade names and code numbers referred to, relate to similar but different FPPs, full details of the differences shall be provided. The proposed trade name shall be such that it does not give rise to confusion with the trade name of already authorised FPP.

Detailed quantitative and qualitative information on the composition of the FPP.

1.3.1. *Composition of the FPP.*

For FPPs the following information shall be reported:

— the content of the technical active substances (based on the specified minimum purity) and the declared content of pure active substances and, where relevant, the corresponding content of the variant (such as salts and esters) of the active substances,

— the content of safeners, synergists and co-formulants,

— the maximum content of relevant impurities, where appropriate.

In addition to the total active substance content, for slow or controlled release FPPs (such as capsule suspension, CS) the free (non-encapsulated) and encapsulated active substance content and the release rate shall be given. Where possible, appropriate Collaborative International Pesticides Analytical Council (CIPAC) methods shall be used. If an alternative method is used this shall be justified by the applicant and a detailed description of the methodology used shall be given.

The concentration of each active substance shall be expressed as follows:

— for solids, aerosols, volatile liquids (maximum boiling point 50 °C) or viscous liquids (lower limit 1 Pa s at 20 °C), as % w/w and g/kg,

— for other liquids/gel formulations, as % w/w and g/l,

— for gases, as % v/v and % w/w.

1.3.2. *Information on the active substances*

For active substances their International Organisation for Standardisation (ISO) common names or proposed ISO common names, their CIPAC numbers, and, where available, the European

Commission (EC) numbers shall be provided. Where relevant, it shall be stated which salt, ester, anion or cation is present.

1.3.3. *Information on safeners, synergists and co-formulants*

Safeners, synergists and co-formulants shall, where possible, be identified both by their chemical name as given both the International Union of Pure and Applied Chemistry (IUPAC) and Chemical Abstracts (CA) nomenclature. Their structural formula shall be provided. For each component of the safeners, synergists and co-formulants the relevant EC number and Chemical Abstracts Service (CAS) number, where they exist, shall be provided. For co-formulants which are mixtures, the composition shall be provided. Where the information provided does not fully identify the safener, synergist or co-formulant, an appropriate specification shall be provided. The trade name, where available, shall also be provided. Safety data sheets shall be provided. They shall be up to date.

For co-formulants the function shall be specified from among the following:

(a) adhesive (sticker);

(b) antifoaming agent;

(c) antifreeze;

(d) binder;

(e) buffer;

(f) carrier;

(g) deodorant;

(h) dispersing agent;

(i) dye;

emetic;

(j) emulsifier;

(k) fertiliser;

(l) preservative;

(m) odourant;

(n) perfume;

(o) propellant;

(p) repellent;

(q) solvent;

(r) stabiliser;

(s) thickener;

(t) wetting agent;

(u) miscellaneous (shall be specified by the applicant).

A description of the formulation process shall be provided.

1.4. Type and code of the FPP

The type and code of FPP shall be designated according to the latest edition of the 'Manual on development and use of FAO and WHO specifications for pesticides' prepared by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS).

Where a FPP is not defined precisely in this publication, a full description of the physical nature and state of the FPP shall be provided, together with a proposal for a suitable description of the type of FPP and a proposal for its definition.

1.5. Function

The function shall be specified from among the following:

(a) acaricide;
(b) other (shall be specified by the applicant).

PHYSICAL, CHEMICAL AND TECHNICAL PROPERTIES OF THE FPP

The extent to which FPPs for which authorisation is sought, comply with relevant FAO/WHO specifications, shall be stated. Divergences from these specifications shall be described in detail, and justified by the applicant.

2.1. Appearance

A description of the colour and of the physical state of the FPP shall be provided.

2.2. Explosive and oxidising properties

The explosive and oxidising properties of FPPs shall be determined and reported. A theoretical estimation based on structure shall be accepted if it meets the criteria set out in Appendix 6 of the United Nations' Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria.

2.3. Flammability and self-heating

The flash point of liquids which contain flammable solvents shall be determined and reported. The flamm- ability of solid FPPs and gases shall be determined and reported. A theoretical estimation based on structure shall be accepted if it meets the criteria set out in Appendix 6 of the United Nations' Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria.

The self-heating shall be determined and reported.

2.4. Acidity/alkalinity and pH value

In the case of aqueous FPPs, the pH value of the neat FPP shall be determined and reported.

In the case of solid and non-aqueous liquid FPPs which are to be applied as aqueous dilutions the pH of a 1 % dilution of the FPP shall be determined and reported.

In the case of FPPs which are acidic (pH < 4) or alkaline (pH > 10) the acidity or alkalinity shall be determined and reported.

2.5. Viscosity and surface tension

For liquid formulations the viscosity shall be determined at two shear rates and at 20°C and 40°C and reported together with the test conditions. The surface tension shall be determined at the highest concentration.

For liquid FPPs containing ≥10 % hydrocarbons and for which the kinematic viscosity is less than 7×10^{-6} m^2/sec at 40 °C the surface tension of the neat formulation shall be determined at 25 °C and reported.

2.6. Relative density and bulk density

The relative density of liquid FPPs shall be determined and reported.

The bulk density (pour and tap) of FPPs which are powders or granules shall be determined and reported.

2.7. Storage stability and shelf-life: effects of temperature on technical characteristics of the FPP

The stability of the FPP after accelerated storage for 14 days at 54 °C shall be determined and reported. Data generated from alternative time/temperature combinations (for example 8 weeks at 40 °C,
12 weeks at 35 °C or 18 weeks at 30 °C) may be submitted as alternative accelerated storage data. Consideration shall be given to performing this test in packaging made of the same material as the commercial packaging.

If the active substance content after the heat stability test has decreased by more than 5 % from the initial value, then information on the breakdown products shall be supplied.

For liquid FPP, the effect of low temperatures on stability shall be determined and reported.

The shelf life of the FPP at ambient temperature shall be determined and reported. Where shelf life is less than two years, the shelf life in months, with appropriate temperature specifications, shall be reported. The ambient temperature stability test shall be performed in packaging made of the same material as the commercial packaging. Where appropriate, data on the content of relevant impurities, before and after storage, shall be provided.

2.8. Technical characteristics of the FPP

The technical characteristics of the FPP shall be determined and reported at appropriate concentrations.

2.8.1. Wettability

The wettability of solid FPPs, which are diluted for use shall be determined and reported.

2.8.2. Persistent foaming

The persistence of foaming of FPPs to be diluted with water shall be determined and reported.

2.8.3. Suspensibility, spontaneity of dispersion and dispersion stability

The suspensibility and the spontaneity of dispersion of water dispersible products shall be determined and reported.
The dispersion stability of FPPs such as aqueous suspo-emulsions (SE), oil-based suspension concentrates (OD) or emulsifiable granules (EG) shall be determined and reported.

2.8.4. Degree of dissolution and dilution stability

The degree of dissolution and the dilution stability of water soluble products shall be determined and reported.

2.8.5. Particle size distribution, dust content, attrition and mechanical stability

2.8.5.1. Particle size distribution

In the case of water dispersible products, a wet sieve test shall be conducted and reported.
The size distribution of particles in the case of powders and suspension concentrates shall be determined and reported.
The nominal size range of granules shall be determined and reported.

2.8.5.2. Dust Content

The dust content of granular FPPs shall be determined and reported.
If results show > 1 % w/w dust then the particle size of the dust generated shall be determined and reported.

2.8.5.3. Attrition

The attrition characteristics of granules and tablets which are loose packed shall be determined and reported.

2.8.5.4. Hardness and Integrity

The hardness and integrity of tablets shall be determined and reported.

2.8.6. Emulsifiability, re-emulsifiability, emulsion stability

The emulsifiability, emulsion stability and re-emulsifiability of FPPs, which exist as emulsions in the spray tank, shall be determined and reported.

Flowability, pourability and dustability

The following characteristics shall be determined and reported:

— the flowability of granular FPPs,

— the pourability of suspensions, and

— the dustability of dustable powders following accelerated storage according to point 2.7.

2.9. Physical and chemical compatibility with other products

The physical and chemical compatibility of recommended tank mixes shall be determined and reported. Known non-compatibility shall be reported.

2.10. Other studies

Supplementary studies necessary for the classification of the FPP by hazard shall be carried out.

PART B: SECTION 3

DATA ON APPLICATION/USE

Data on application shall be submitted and shall be consistent with good practice.

3.1. Proposed Indications

The proposed indications of use shall be specified including the target species and effects achieved.

3.2. Effects on pests

The nature of the effects on pests shall be stated:

(a) contact action;

(b) stomach action;

(c) inhalation action;

(d) desiccant;

(e) reproduction inhibitors;

(f) other (shall be specified by the applicant).

In addition, it shall be specified whether the FPP is systemic or not.

3.3. Application rate and concentration of the active substance

For each method of application and each use, the rate of application per unit treated, for FPP in g, kg, mL or L shall be provided.

3.4. Method of application

The method of application proposed shall be described fully, indicating the type of equipment to be used, if any, as well as the type and volume of diluent to be used.

3.5. Number and timing of applications and duration of protection

The maximum number of applications to be used and their timing shall be reported.
The duration of protection afforded both by each application and by the maximum number of applications to be used, shall be indicated.

3.6. Proposed instructions for use

The proposed instructions for use of the FPP, to be printed on labels and leaflets, shall be provided.

PART B: SECTION 4

FURTHER INFORMATION ON THE FPP

4.1. Safety intervals and other precautions to protect humans, animals and the environment

The information provided shall follow from and be supported by the data provided for the active substances and that provided in accordance with Sections 7 and 8.

4.2. Recommended methods and precautions

The recommended methods and precautions concerning washing/cleaning of machinery and protective equipment, detailed handling procedures for the storage, at both warehouse and user level of FPPs, for their transport and in the event of fire shall be provided by the applicant. The effectiveness of cleaning procedures shall be described in detail. Where available, information on combustion products shall be provided. The risks likely to arise and the methods and procedures to minimise the hazards arising, shall be specified. Procedures to preclude or minimise the generation of waste or leftovers shall be provided.

Where appropriate, the nature and characteristics of protective clothing and equipment proposed shall be provided. The data provided shall be sufficient to evaluate the suitability and effectiveness under realistic conditions of use.

4.3. Emergency measures in the case of an accident

Detailed procedures to be followed in the event of an emergency, whether arising during transport, storage or use, shall be provided and include:

(a) containment of spillages;

(b) decontamination of areas, vehicles and buildings;

(c) disposal of damaged packaging, absorbents and other materials;

(d) protection of emergency workers and residents, including bystanders;

(e) first aid measures.

4.4. Packaging, compatibility of the FPP with proposed packaging materials

Packaging to be used shall be fully described and specified in terms of the materials used, manner of construction (for example extruded, welded), size and capacity, wall thickness, size of opening, type of closure and seals. Packaging shall be designed in order to limit as much as possible exposure of operators and of the environment.

All packaging used shall comply with the relevant Union legislation on transportation and safe handling.

4.5. Procedures for destruction or decontamination of the FPP and its packaging

Procedures for destruction and decontamination shall be developed for both small quantities (user level) and large quantities (warehouse level). The procedures shall be consistent with provisions in place relating to the disposal of waste and of toxic waste. The proposed means of disposal shall be without unacceptable influence on the environment and be the most cost effective and feasible.

4.5.1. Neutralisation procedures

Neutralisation procedures (such as by reaction with other substances to form less toxic compounds) for use in the event of accidental spillages shall be described, where such procedures can be applied. The products produced after neutralisation shall be practically or theoretically evaluated and reported.

Controlled incineration

Chemical active substances as well as FPPs containing them, contaminated materials, or contaminated packaging shall be disposed of through controlled incineration in a licensed incinerator.

If controlled incineration is not the preferred method of disposal, full information on the alternative method of safe disposal used shall be provided. Data shall be provided for such methods, to establish their effectiveness and safety.

PART B: SECTION 5

ANALYTICAL METHODS

Introduction

The provisions of this Section cover analytical methods used for the generation of pre-authorisation data and required for post-authorisation control and monitoring purposes.

Descriptions of methods shall be provided and include details of equipment, materials and conditions used. On request, the following shall be provided:

(a) analytical standards of the purified active substance and of the FPP;

(b) samples of the active substance as manufactured;

(c) analytical standards of relevant metabolites and all other components included in all monitoring residue definitions;

(d) samples of reference substances for the relevant impurities.

In addition, the standards referred to in points (a) and (c) shall, where possible, be made commercially available and, on request, the distributing company shall be named.

5.1. Methods used for the generation of pre-authorisation data

5.1.1. Methods for the analysis of the FPP

Methods shall be provided, with a full description, for the determination of:

(a) active substance and/or variant in the FPP;

(b) relevant impurities identified in the technical material or which may be formed during manufacture of the FPP or from degradation of the FPP during storage;

(c) relevant co-formulants or components of co-formulants, where required by the national competent authorities.

In the case of a FPP containing more than one active substance and/or variant a method capable of determining each, in the presence of the other, shall be provided. If a combined method is not submitted, the technical reasons shall be stated.

The applicability of CIPAC methods shall be assessed and reported. In case of use of a CIPAC method, further validation data shall not be required, but example chromatograms shall be submitted, where available.

The specificity of the methods shall be determined and reported. In addition, the extent of interference by other substances present in the FPP (such as impurities or co-formulants), shall be determined.

The linearity of methods shall be determined and reported. The calibration range shall extend (by at least 20 %) beyond the highest and lowest nominal content of the analyte in relevant analytical solutions. Either duplicate determinations at three or more concentrations or single determinations at five or more concentrations shall be made. The equation of the calibration line and the correlation coefficient shall be reported and a typical calibration plot shall be submitted. In cases where a non-linear response is used, this shall be justified by the applicant.

The precision (repeatability) of the methods shall be determined and reported. A minimum of five replicate sample determinations shall be made, and the mean, the relative standard deviation

and the number of determinations shall be reported. The accuracy of the methods shall be determined on at least two representative samples at levels appropriate to the material specification. The mean and the relative standard deviation of the recoveries shall be reported.

For relevant impurities and, where necessary, for relevant co-formulants the limit of quantification (LOQ) shall be determined and reported and shall be at a concentration of analyte, which is of toxicological or environ- mental significance, or at the concentration which is formed during storage of the product, where relevant.

5.1.2. Methods for the determination of residues

Methods shall be submitted, with a full description, for the determination of non-isotope-labelled residues in all areas of the dossier, as set out in detail in the following points:

(a) in soil, water, sediment, air and any additional matrices used in support of environmental fate studies;

(b) In feed, body fluids and tissues, air and any additional matrices used in support of toxicology studies;

(c) in body fluids, air and any additional matrices used in support of operator, worker, resident and bystander exposure studies;

(d) in food of animal origin, feed and any additional matrices used in support of residues studies;

(e) in soil, water, sediment, feed and any additional matrices used in support of ecotoxicology studies;

(f) in water, buffer solutions, organic solvents and any additional matrices resulting from the physical and chemical properties tests.

The specificity of the methods shall be determined and reported. Validated confirmatory methods shall be submitted if appropriate.

The linearity, recovery and precision (repeatability) of methods shall be determined and reported.

Data shall be generated at the LOQ and either the likely residue levels or ten times the LOQ. The LOQ shall be determined and reported for each component in the residue definition.

5.2. Methods for post-authorisation control and monitoring purposes

As far as practicable these methods shall employ the simplest approach, involve the minimum cost, and require commonly available equipment.

Analytical methods for the determination of the active substance and relevant impurities in the FPP shall be submitted, unless the applicant shows that these methods already submitted in accordance with the requirements set out in point 5.1.1 can be applied.

The provisions set out in point 5.1.1 shall apply.

Methods, with a full description, shall be submitted for the determination of residues:

— in food and feed of plant and animal origin,

— in body fluids and tissues,

— in soil,

— in water,

— in air, unless the applicant shows that exposure of operators, workers, residents or bystanders is negligible.

The applicant may deviate from such requirement by showing that the methods submitted in accordance with the requirements set out in point 4.2 of Part A of this guidelines can be applied.

The specificity of the methods shall enable all components included in the monitoring residue definition to be determined. Validated confirmatory methods shall be submitted if appropriate.

The linearity, recovery and precision (repeatability) of methods shall be determined and reported.

Data shall be generated at the LOQ and either the likely residue levels or ten times the LOQ. The LOQ shall be determined and reported for each component included in the monitoring residue definition.

For residues in or on food and feed animal origin and residues in drinking water, the repro- ducibility of the method shall be determined by means of an independent laboratory validation (ILV) and reported.

PART B: SECTION 6

EFFICACY DATA

Introduction

1. The data supplied shall be sufficient to permit an evaluation of the FPP to be made. It shall be possible to evaluate the nature and extent of benefits that accrue following use of the FPP, in comparison to an untreated control and where they exist in comparison to suitable reference products and damage thresholds, and to define its conditions of use.

2. The number of trials to be conducted and reported shall reflect factors such as the extent to which the properties of the active substances it contains are known and on the range of conditions that arise, including variability in animal health conditions, climatic differences, the range of production practices, the mode of application the type of pests and the type of FPP.

3. Sufficient data shall be submitted to confirm that patterns of use of the FPP are representative of the regions and the range of conditions, likely to be encountered in Kenya, for which its use is intended. Where the applicant claims that tests in one or more of the proposed regions of use are unnecessary because conditions are comparable with those in other regions where tests have been carried out, the applicant shall substantiate the claim for comparability with documentary evidence.

4. In order to assess seasonal differences, if any, sufficient data shall be generated and submitted to confirm the performance of the FPP in each climatically different region for each particular combination.

6.1. Preliminary tests

Reports in summary form of preliminary tests, including in vitro and field studies, used to assess the biological activity or dose range finding of the FPP and of the active substances it contains, shall be submitted as relevant when requested by VMD. These reports shall provide additional information to justify the recommended dose of the FPP and, where the FPP contains more than one active substance, the ratio of the active substances.

6.2. Testing effectiveness

The tests shall provide sufficient data to permit an evaluation of the level, duration and consistency of control or protection or other intended effects of the FPP in comparison to suitable reference products, where they exist.

Test conditions

A trial shall, where possible, consist of the following three components: test product, reference product and untreated control.

The performance of the product shall be investigated in relation to suitable reference products, where they exist. A product shall be considered a suitable reference product if it fulfils the following requirements: it is authorised and has proved a sufficient performance in practice under the conditions of the area of intended use. The working spectrum, time and method of application, mode of action shall be close to those of the tested FPP. If this is not possible, reference product and test product shall be applied according to their specified use.

A FPP shall be tested in circumstances where the target pest has been shown to have been present at a level causing or known to cause adverse effects on an animal or where the pest is present at such a level that an evaluation of the product can be made.

In order to clarify the dose response, dose rates lower than the recommended one shall be included in some trials in order to enable assessment of whether the recommended rate is the minimum

necessary to achieve the desired effect.

The duration of the effects of treatment shall be investigated in relation to the control of the target organism or effect on the animal, as appropriate. When more than one application is recommended for the proposed use pattern of the product, trials shall be reported, which establish the duration of the effects of an application, the number of applications necessary and the desired intervals between them.

Evidence shall be submitted to show that the dose, timing and method of application recommended give adequate control, protection or have the intended effect in the range of circumstances likely to be encountered in practical use.

If there is clear evidence that the performance of the FPP is likely to be affected by environmental factors, such as temperature or rain, an investigation of the effects of such factors on performance shall be carried out and reported, particularly where it is known that the performance of chemically related products is so affected.

Where proposed label claims include recommendations for the use of the FPP with other FPPs or adjuvants information on the performance of the mixture shall be provided.

Trials shall be designed to investigate specified issues, to minimise the effects of random variation between different parts of each animal and to enable statistical analysis to be applied to results amenable to such analysis. The design, analysis, conduct and reporting of trials shall be in accordance with the specific standards. The report shall include a detailed and critical assessment of the data.
A statistical analysis of results amenable to such analysis shall be carried out; where necessary the test guideline used shall be adapted to enable such analysis.
Where relevant, evidence of yield and quality may be required as a demonstration of effectiveness.

6.3. Information on the occurrence or possible occurrence of the development of resistance

Laboratory data and where it exists, field information relating to the occurrence and development of resistance or cross-resistance in populations of pests to the active substances, or to related active substances, shall be provided. Where such information is not directly relevant to the uses for which authorisation is sought or to be renewed, it shall, if available, nevertheless be provided in summary form, as it may provide an indication of the likelihood of resistance developing in the target population.

Where there is evidence or information to suggest that, in commercial use, the development of resistance is likely, evidence shall be generated and submitted as to the sensitivity of the population of the harmful organism concerned to the FPP. In such cases a management strategy designed to minimise the likelihood of resistance developing in target species shall be provided. This management strategy shall have regard for and refer to any relevant existing strategies and restrictions already in place.

6.4. Adverse effects

6.4.1. Toxicity to animals

The test shall provide sufficient data to permit an evaluation of the performance of the FPP and of the possible occurrence of toxicity after treatment with the product.

SECTION 7

TOXICOLOGICAL STUDIES

Introduction

1. For the evaluation of the toxicity of the FPP information shall be provided on acute toxicity, irritation and sensitisation of the active substance. Where available, information on mode of toxic action, toxicological profile and all other known toxicological aspects of the active substance and of substances of concern, shall be submitted.

2. Consideration shall be given to the possible effects of components on the toxic potential of the total mixture.

7.1. Acute toxicity

The studies, data and information to be provided and evaluated, shall be sufficient to permit the identification of effects following a single exposure to the FPP, to be assessed, and in particular to establish, or indicate:

(a) the toxicity of the product;
(b) toxicity of the product relative to the active substance;
(c) the time course and characteristics of the effect with full details of behavioural changes and possible gross pathological findings at post-mortem;
(d) where possible the mode of toxic action; and
(e) the relative hazard associated with the different routes of exposure.

While the emphasis shall be on estimating the toxicity ranges involved, the information generated shall also permit the FPP to be classified.

7.1.1. Oral toxicity

Circumstances in which required

A test for acute oral toxicity shall be carried out, unless the applicant can justify an alternative approach. In the latter case, acute oral toxicity of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the toxic potential of the total mixture.

7.1.2. Dermal toxicity

Circumstances in which required

A test for dermal toxicity shall be carried out on a case by case basis, unless the applicant can justify an alternative approach. In the latter case, acute dermal toxicity of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the toxic potential of the total mixture.

Findings of severe skin irritation or corrosion in the dermal study may be used instead of performing a specific irritation study.

7.1.3. Inhalation toxicity

The study shall provide the inhalation toxicity to rats of the FPP or of the smoke it generates.

Circumstances in which required

The study shall be carried out where the FPP:

(a) is a gas or liquified gas;

(b) is a smoke generating product or fumigant;
(c) is used with fogging/misting equipment;
(d) is a vapour releasing FPP;
(e) is supplied in an aerosol dispenser;
(f) is in a form of a powder or granules containing a significant proportion of particles of diameter < 50 μm (> 1 % on a weight basis);
(g) contains an active substance with a vapour pressure > 1×10^{-2} Pa and is to be used in enclosed spaces such as warehouses or glasshouses;
(h) is to be applied by spraying.

A study shall not be required if the applicant can justify an alternative approach, where applicable. For this purpose, acute inhalation toxicity of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the toxic potential of the total mixture.

The head/nose only exposure shall be used, unless whole body exposure can be justified.

7.1.4. Skin irritation

The results of the study shall provide the potential for skin irritancy of the FPP including the potential reversibility of the effects observed.
Before undertaking *in vivo* studies for corrosion/irritation of the FPP, a weight-of-evidence analysis shall be performed on the existing relevant data. Where insufficient data are available, they can be developed through application of sequential testing.
The testing strategy shall follow a tiered approach:
(1) the assessment of dermal corrosivity using a validated *in vitro* test method;
(2) the assessment of dermal irritation using a validated *in vitro* test method (such as human reconstituted skin models);
(3) an initial *in vivo* dermal irritation study using one animal, and where no adverse effects are noted;
(4) confirmatory testing using one or two additional animals.

Consideration shall be given to use the dermal toxicity study to provide irritancy information. Findings of severe skin irritation or corrosion in the dermal study may be used instead of performing a specific irritation study.

Circumstances in which required

The skin irritancy of the FPP shall be reported based on the tiered approach, unless the applicant can justify an alternative approach. In the latter case, skin irritation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the irritant potential of the total mixture.

7.1.5. Eye irritation

The results of the study shall provide the potential for eye irritation of the FPP, including the potential reversibility of the effects observed.
Before undertaking *in vivo* studies for eye corrosion/irritation of the FPP, a weight-of- evidence analysis shall be performed on the existing relevant data. Where available data are considered insufficient, further data may be developed through application of sequential testing.
The testing strategy shall follow a tiered approach:
(1) the use of an *in vitro* dermal irritation/corrosion test to predict eye irritation/corrosion;
(2) the performance of a validated or accepted *in vitro* eye irritation study to identify severe eye irritants/ corrosives (such as BCOP, ICE, IRE, HET-CAM), and where negative results are obtained;
(3) the assessment of eye irritation using an available, *in vitro* test method validated for FPPs for identification of non-irritants or irritants, and when not available;

(4) an initial *in vivo* eye irritation study using one animal, and where no adverse effects are noted;
(5) confirmatory testing using one or two additional animals.

Circumstances in which required

Eye irritation tests shall be provided, unless it is not likely that severe effects on the eyes may be produced or the applicant can justify an alternative approach. In the latter case, eye irritation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the irritant potential of the total mixture.

7.1.6. Skin sensitisation

The study shall provide information to assess the potential of the FPP to provoke skin sensitisation reactions.

Circumstances in which required

The skin sensitisation test shall be carried out unless the active substances or co-formulants are known to have sensitising properties or the applicant can justify an alternative approach. In the latter case, skin sensitisation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the sensitising potential of the total mixture.

The local lymph node assay (LLNA) shall be used, including where appropriate the reduced variant of the assay. In case the LLNA cannot be conducted, a justification shall be provided and the Guinea Pig Maxi- misation Test shall be performed. Where a guinea pig assay (Maximisation or Buehler), meeting OECD guidelines and providing a clear result, is available, further testing shall not be carried out for animal welfare reasons.

Since a skin sensitiser can potentially induce hypersensitivity reaction, potential respiratory sensitisation shall be taken into account when appropriate tests are available or when there are indications of respiratory sensitisation effects.

7.1.7. Supplementary studies for combinations of FPPs

In cases where the product label includes requirements for use of the FPP with other FPPs or with adjuvants as a tank mix, it may be necessary to carry out studies for a combination of FPPs or for the FPP with adjuvant. The for supplementary studies shall be considered on a case by case basis, taking into account the results of the acute toxicity studies of the individual FPPs and the toxicological properties of the active substances, the possibility for exposure to the combination of the products concerned, with particular regard to vulnerable groups, and available information or practical experience with the products concerned or similar products.

7.2 Data on exposure

For the purpose of this guidelines the following definitions apply:
(a) operators are people who are involved in activities relating to the application of a FPP, such as mixing, loading, application, or relating to cleaning and maintenance of equipment containing a FPP; operators may be professionals or amateurs;
(b) workers are people who, as part of their employment, enter an area that has previously been treated with a FPP or who handle a crop that has been treated with a FPP;
(c) bystanders are people who casually are located within or directly adjacent to an area where

application of a FPP is in process or has taken place, but not for the purpose of working on the treated area or with the treated commodity;

(d) residents are people who live, work or attend any institution near to areas that are treated with FPPs, but not for the purpose of working on the treated area or with the treated commodity.

In cases where the product label includes requirements for use of the FPP with other FPPs or with adjuvants as a tank mix, the exposure assessment shall cover the combined exposure. Cumulative and synergistic effects shall be taken into account and reported in the dossier.

7.2.1. *Operator exposure*

Information shall be provided to permit an assessment of the extent of exposure to the active substances and toxicologically relevant compounds in the FPP likely to occur under the proposed conditions of use, taking into account cumulative and synergistic effects. It shall also provide a basis for the selection of the appropriate protective measures including personal protective equipment to be used by operators and to be specified on the label.

7.2.1.1. Estimation of operator exposure

An estimation shall be made, using where available a suitable calculation model, in order to permit an evaluation of the operator exposure likely to arise under the proposed conditions of use. Where relevant, this estimation shall take into account cumulative and synergistic effects resulting from the exposure to more than one active substance and toxicologically relevant compounds, including those in the product and tank mix.

Circumstances in which required

An estimation of operator exposure shall always be performed.

Estimation conditions

An estimation shall be made for each type of application method and application equipment proposed for use of the FPP for handling the undiluted or diluted product.
The estimation shall address mixing/loading and application, and shall include clean-up activities and routine maintenance of the application equipment. Specific information on local use conditions (types and sizes of containers to be used, application equipment, typical work rates and application rates, spray concentration, field sizes, crop growing climatic conditions) shall be included.
At first an estimation shall be made with the assumption that the operator is not using any personal protective equipment.
Where appropriate, a further estimation shall be made with the assumption that the operator is using effective and readily obtainable protective equipment, which is feasible to be used in practice.
Where protective measures are specified on the label, the estimation shall take these into account.

7.2.1.2. Measurement of operator exposure

The study shall provide data to permit an evaluation of the operator exposure likely to arise under the specific proposed conditions of use. The study shall be ethically sound.

Circumstances in which required

Exposure data for the relevant exposure routes shall be reported where there are no representative data in available calculation models or where the model-based risk assessment indicates that the relevant reference value is exceeded.

This will be the case, where the results of the estimation of operator exposure in accordance with point 7.2.1.1 indicate that one or both of the following conditions are fulfilled:

(a) the AOEL established in the context of approval of the active substance may be

exceeded;

(b) the Limit Values established for the active substance and toxicologically relevant compounds of the FPP.

The study shall be done under realistic exposure conditions taking into account the proposed conditions of use.

7.2.2. Bystander and resident exposure

Information shall be provided to permit an assessment of the extent of exposure to the active substances and toxicologically relevant compounds likely to occur under the proposed conditions of use, taking into account, where relevant, cumulative and synergistic effects. It shall also provide a basis for the selection of appropriate protective measures, including restricted entry intervals, exclusion of residents and bystanders from treatment areas and separation distances.

7.2.2.1 Estimation of bystander and resident exposure

An estimation shall be made, using where available a suitable calculation model in order to permit an evaluation of the bystander and resident exposure likely to arise under the proposed conditions of use. Where relevant, this estimation shall take into account cumulative and synergistic effects resulting from the exposure to more than one active substance and toxicologically relevant compounds, including those in the product and tank mix.

The applicant shall take into consideration that bystanders can be exposed during or after the application of FPPs and residents may be exposed to FPPs, mainly, but not only, by inhalation and dermal route and that infants and toddlers exposure may also occur by the oral route (through hand-mouth transfer).

Circumstances in which required

An estimation of bystander and resident exposure shall always be performed.

Estimation conditions

An estimation of bystander and resident exposure shall be made for each relevant type of application method. Specific information including maximum total dose and spray concentration shall be included. The estimation shall be made with the assumption that bystanders and residents do not use any personal protective equipment.

7.2.2.2. Measurement of bystander and resident exposure

The study shall provide data to permit an evaluation of the bystander and resident exposure likely to arise under the specific proposed conditions of use. The study shall be ethically sound.

Circumstances in which required

Exposure data for the relevant exposure routes shall be required where the model based risk assessment indicates that the relevant reference value is exceeded or where there are no representative data in available calculation models.
The study shall be done under realistic exposure conditions taking into account the proposed conditions of use.

7.2.3. Worker exposure

Information shall be provided to permit an assessment of the extent of exposure to the active substances and toxicologically relevant compounds in the FPP likely to occur under the proposed conditions of use and agricultural practices, taking into account cumulative and synergistic effects. It shall also provide a basis for the selection of appropriate protective

measures, including waiting and re-entry periods.

7.2.3.1. Estimation of worker exposure

An estimation shall be made using, where available, a suitable calculation model, in order to permit an evaluation of the worker exposure likely to arise under the proposed conditions of use. Where relevant, this estimation shall take into account cumulative and synergistic effects resulting from the exposure to more than one active substance and toxicologically relevant compounds, including those in the product and tank mix.

Circumstances in which required

The estimation of worker exposure shall be completed when such exposure could arise under the proposed conditions of use.

Estimation conditions

An estimation of worker exposure shall be made for crops and tasks to be carried out. Specific information including description of post-applications activities, exposure duration, application rate, number of appli- cations, minimum spray interval and growth stage, shall be provided. If data on the amount of dislodgeable residues under the proposed conditions of use are not available, default assumptions shall be used.

At first, the estimation shall be made using available data on the exposure to be expected with the assumption that the worker is not using any personal protective equipment. Where appropriate, a second estimation shall be made with the assumption that the worker is using effective and readily obtainable protective equipment which is feasible to be used and will be worn habitually by workers, for example because it was necessitated by other aspects of task being undertaken.

7.2.3.2. Measurement of worker exposure

The study shall provide data to permit an evaluation of the worker exposure likely to arise under the proposed conditions of use. The study shall be ethically sound.

Circumstances in which required

Exposure data for the relevant exposure routes shall be reported where the model based risk assessment indicates that the relevant reference value is exceeded or where there are no representative data in available calculation models.
This will be the case, where the results of the estimation of worker exposure in accordance with point 7.2.3.1 indicate that one or both of the following conditions are fulfilled:

(a) the AOEL established in the context of approval of the active substance may be exceeded;
(b) the Limit Values established for the active substance and toxicologically relevant compounds of the FPP may be exceeded.

The study shall be done under realistic exposure conditions taking into account the proposed conditions of use.

7.3. Dermal absorption

The studies shall provide a measurement of the absorption through the skin of the active substances and toxicologically relevant compounds in the FPP to be authorised.

Circumstances in which required

The study shall be conducted when dermal exposure is a significant exposure route, and no acceptable risk is estimated using default absorption value.

Test conditions

Data from absorption studies, preferably using human skin *in vitro*, shall be reported.
Studies shall be performed on representative FPPs at both in use dilution (when applicable) as well as the concentrated form.
In case studies do not correspond with the anticipated exposure situation (for example with regard to the type of co-formulant or the concentration), scientific argument shall be provided before such data can be used with confidence.

7.4. Available toxicological data relating to co-formulants

PARTB: SECTION 8

RESIDUES IN FOOD AND FEED

Data and information on residues in or on treated products, food and feed in accordance with Section 6 of Part A of this guideline shall be submitted, unless the applicant shows that the data and information already submitted for the active substance can be applied.

PART B: SECTION 9

FATE AND BEHAVIOUR IN THE ENVIRONMENT

Introduction

1. Predicted environmental concentrations (PEC).

1.1. A realistic worst-case estimation shall be made of the expected concentrations of the active substance and metabolites, breakdown and reaction products:

— which account for more than 10 % of the amount of active substance added,

— which account for more than 5 % of the amount of active substance added, in at least two sequential measurements,

— for whose individual components (> 5 %) the maximum of formation is not yet reached at the end of the study, in soil, surface in soil, groundwater, surface water, sediment and air, following use as proposed or already occurring.

1.2. For the purposes of the estimation of such concentrations the following definitions apply:

(a) Predicted environmental concentration in soil (PEC_S): the level of residues in the top layer of the soil and to which non-target soil organisms may be exposed (acute and chronic exposure).

(b) Predicted environmental concentration in surface water (PEC_{SW}): the level of residues, in surface water to which non-target organisms may be exposed (acute and chronic exposure).

(c) Predicted environmental concentration in sediment (PEC_{SED}): the level of residues, in sediment to which non-target benthic organisms may be exposed (acute and chronic exposure).

(d) Predicted environmental concentration in groundwater (PEC_{GW}): the level of residues in groundwater.

(e) Predicted environmental concentration in air (PEC_A): the level of residues in air, to

which man, animals and other non-target organisms may be exposed (acute and chronic exposure).

1.3. For the estimation of these concentrations all relevant information on the FPP and on the active substance shall be taken into account. Where relevant the parameters set out in Section 7 of Part A of this guideline shall be used.

1.4. When models are used for estimation of predicted environmental concentrations they shall:

— make a best-possible estimation of all relevant processes involved taking into account realistic parameters and assumptions,

— where possible be reliably validated with measurements carried out under circumstances relevant for the use of the model,

— be relevant to the conditions in the area of use.

1.5. The information provided shall, where relevant, include that referred to in Section 7 of Part A of this guideline.

9.1. Fate and behaviour in soil

9.1.1. Rate of degradation in soil

9.1.1.1. Laboratory studies

Laboratory studies on soil degradation shall provide best possible estimates of the time required for degra- dation of 50 % and 90 % ($DegT50_{lab}$ and $DegT90_{lab}$) of the active substance under laboratory conditions.

Circumstances in which required

The persistence and behaviour of FPPs in soil shall be investigated unless it is possible to extrapolate from data obtained on the active substance and metabolites, breakdown and reaction products in accordance with the requirements set out in point 7.1.2.1 of Part A of this guideline. Where it is not possible to extrapolate from anaerobic incubation data obtained on the active substance and metabolites, breakdown and reaction products in accordance with the requirements set out in point 7.1.2.1 of Part A of this guideline, an anaerobic degradation study shall be submitted unless the applicant shows that exposure of the FPP containing the active substance to anaerobic conditions is unlikely to occur for the intended uses.

Test conditions

Studies on the rate of aerobic degradation of the active substance shall be reported for at least four soils. Soil properties shall be comparable to those used for the aerobic studies performed in accordance with point 7.1.1 and 7.1.2.1 of Part A of this guideline. Reliable DegT50 and 90 values shall be available for a minimum of four different soils.
Studies on the rate of anaerobic degradation of the active substance shall be carried out using the same procedure and comparable soil as for the anaerobic study performed in accordance with point 7.1.1.2 of Part A of this guideline.
The kinetic formation fraction and degradation rates of potentially relevant metabolites shall be established, in the studies under both aerobic and anaerobic conditions by extension of the study for the active substance, where it is not possible to extrapolate from points 7.1.2.1.2 and 7.1.2.1.4 of Part A of this guideline.
In order to assess the influence of temperature on degradation, a calculation with an adequate Q10 factor or an adequate number of additional studies at a range of temperatures shall be performed.
Reliable DegT50 and 90 values for metabolites, breakdown and reaction products shall be provided for at least three soils from the studies under aerobic conditions.

9.1.1.2. Field studies

9.1.1.2.1. Soil dissipation studies

The soil dissipation studies shall provide best-possible estimates of the time taken for dissipation of 50 % and 90 % ($DisT50_{field}$ and $DisT90_{field}$) and if possible the time taken for degradation of 50 % and 90 % ($DegT50_{field}$ and $DegT90_{field}$), of the active substance under field conditions. Where relevant, information on metabolites, breakdown and reaction products shall be reported.

Circumstances in which required

The dissipation and behaviour of FPPs in soil shall be investigated unless it is possible to extrapolate from data obtained on the active substance and metabolites, breakdown and reaction products in accordance with the requirements set out in point 7.1.2.2.1 of Part A of this guideline.

Test conditions

Individual studies on a range of representative soils (normally at least four different types at different geographical locations) shall be continued until at least 90% of the amount applied has dissipated from the soil or been transformed to substances that are not the subject of the investigation.

9.1.1.2.2. Soil accumulation studies

The tests shall provide sufficient data to evaluate the possibility of accumulation of residues of the active substance and of metabolites, breakdown and reaction products.

Circumstances in which required

Soil accumulation studies shall be reported unless it is possible to extrapolate from data obtained on the active substance and metabolites, breakdown and reaction products in accordance with the requirements set out in point 7.1.2.2.2 of Part A of this guideline.

Test conditions

Long term field studies shall be performed on at least two relevant soils at different geographical locations and involve multiple applications.

9.1.2. Mobility in soil

The information made available shall provide sufficient data to evaluate the mobility and leaching potential of the active substance and metabolites, breakdown and reaction products.

9.1.2.1. Laboratory studies

Circumstances in which required

The mobility of FPPs in soil shall be investigated unless it is possible to extrapolate from data obtained in accordance with the requirements set out in points 7.1.2 and 7.1.3.1 of Part A of this guideline.

Test conditions

The same provisions as provided under points 7.1.2 and 7.1.3.1 of Part A of this guideline apply.

9.1.2.2. Lysimeter studies

Lysimeter studies shall be performed, where necessary, to provide information on:
— the mobility in soil,
— the potential for leaching to ground water,
— the potential distribution in soil.

Circumstances in which required

The decision whether lysimeter studies are to be carried out, as an experimental outdoor study in the framework of a tiered leaching assessment scheme shall take into account the results of degradation and mobility studies and the calculated PEC_{GW}. The type of study to be conducted shall be discussed with the national competent authorities.
These studies shall be performed unless it is possible to extrapolate from data obtained on the active substance and metabolites, breakdown and reaction products in accordance with the requirements set out in point 7.1.4.2 of Part A of this guideline.

Test conditions

Studies shall cover the realistic worst case situation, and the duration necessary for observation of potential leaching, taking into account the soil type, climatic conditions, the application rate and the frequency and period of application.
Water percolating from soil columns shall be analysed at suitable intervals, while residues in plant material shall be determined at harvest. Residues in the soil profile in at least five layers shall be determined on termination of experimental work. Intermediate sampling shall be avoided, since removal of plants (except for harvesting in accordance with normal agricultural practice) and soil influence the leaching process.

Precipitation, soil and air temperatures shall be recorded at regular intervals, at least on a weekly base.

The depth of the lysimeters shall be at least 100 cm. The soil cores shall be undisturbed. Soil temperatures shall be similar to those pertaining in the field. Where necessary, supplementary irrigation shall be provided to ensure optimal plant growth and to ensure that the quantity of percolation water is similar to that in the regions for which authorisation is sought. When during the study the soil has to be disturbed for agricultural reasons it shall not be disturbed deeper than 25 cm.

9.1.2.3. Field leaching studies

Field leaching studies shall be performed, where necessary, to provide information on:

— the mobility in soil,

— the potential for leaching to ground water,

— the potential distribution in soil.

Circumstances in which required

The decision whether field leaching studies are to be carried out, as an experimental outdoor study in the framework of a tiered leaching assessment scheme shall take into account the calculated PEC_{GW} and the results of degradation and mobility studies. The type of study to be conducted shall be discussed with the national competent authorities. These studies shall be performed unless it is possible to extrapolate from data obtained on the active substance and metabolites, breakdown and reaction products in accordance with the requirements set out in point 7.1.4.3 of Part A of the this guideline.

Test conditions

Studies shall cover the realistic worst case situation, taking into account the soil type, climatic conditions, the application rate and the frequency and period of application.
Water shall be analysed at suitable intervals. Residues in the soil profile in at least five layers shall be determined on termination of experimental work. Intermediate sampling of plant and soil material shall be avoided (except for harvesting in accordance with normal agricultural practice), since removal of plants and soil influence the leaching process.

Precipitation, soil and air temperatures shall be recorded at regular intervals (at least on a weekly base).

Information on the groundwater table in the experimental fields shall be submitted. Depending on the experimental design, a detailed hydrological characterisation of the test field shall be carried out. If soil cracking is observed during the study this shall be fully described.

Attention shall be given to the number and the location of water collection devices. The placement of these devices in the soil shall not result in preferential flow paths.

9.1.3. Estimation of concentrations in soil

PEC_S estimations shall relate both to a single application at the highest rate of application for which auth- orisation is sought, and to the maximum number at the shortest interval and highest rates of application for which authorisation is sought, and shall be expressed in terms of mg of active substance per kg of dry soil.
The factors which shall be considered in making PEC_S estimations relate to direct and indirect application to soil, drift, run off, and leaching and include processes such as volatilisation, adsorption, hydrolysis, photolysis, aerobic and anaerobic degradation. Appropriate soil layer depths shall be used depending on the application method and soil cultivation. Where ground cover is present at time of application, the impact of crop interception in reducing soil exposure may be included in estimations.

Initial PEC_S, immediately after application, shall be provided for the active substance, metabolites, breakdown and reaction products. Appropriate short-term and long-term PEC_S calculations (time weighted averages) shall be provided for the active substance, metabolites, breakdown and reaction products with respect to data from ecotoxicological studies.

Calculation of plateau concentrations in soil shall be provided where on the basis of soil dissipation studies it is established that DisT90 > one year, and where repeated application is envisaged, whether in the same growing season or in succeeding years.

9.2. Fate and behaviour in water and sediment

9.2.1. Aerobic mineralisation in surface water

Circumstances in which required

The persistence and behaviour of FPPs in open water (freshwater, estuarine and marine) shall be investigated unless it is possible to extrapolate from data obtained on the active substance and metabolites, breakdown and reaction products in accordance with the requirements set out in point 7.2.2.2 of Part A of this guideline.

The test shall be reported unless the applicant shows that contamination of open water will not occur.

Test conditions

The rate of degradation and the pathway or pathways shall be reported either for a 'pelagic' test system or for a 'suspended sediment' system. Where relevant, additional test systems, which differ with respect to organic carbon content, texture or pH shall be used.

Results obtained shall be presented in the form of schematic drawings showing the pathways involved, and in the form of balance sheets which show the distribution of radio-label in water and, where relevant, sediment as a function of time, as between:

(a) active substance;
(b) CO_2;
(c) volatile compounds other than CO_2;
(d) individual identified transformation products;
(e) extractable substances not identified; and
(f) non-extractable residues in sediment.

The duration of the study shall not exceed 60 days unless the semi-continuous procedure with periodical renewal of the test suspension is applied. However, the period for the batch test may be extended to a maximum of 90 days, if the degradation of the test substance has started within the first 60 days.

9.2.2. Water/sediment study

Circumstances in which required

The persistence and behaviour of FPPs in aquatic systems shall be investigated unless it is possible to extrapolate from data obtained on the active substance and metabolites, breakdown and reaction products in accordance with the requirements set out in point 7.2.2.3 of Part A of these guidelines.

The test shall be reported unless the applicant shows that contamination of surface water will not occur.

Test conditions

The degradation pathway or pathways shall be reported for two water/sediment systems. The two sediments selected shall differ with respect to organic carbon content and texture, and where relevant, with respect to pH.

Results obtained shall be presented in the form of schematic drawings showing the pathways involved, and in the form of balance sheets which show the distribution of radio-label in water and sediment as a function of time, as between:

active substance;
(a) CO_2;
(b) volatile compounds other than CO_2;
(c) individual identified transformation products;
(d) extractable substances not identified; and
(e) non-extractable residues in sediment.

The duration of the study shall be at least 100 days. It shall be longer where this is necessary to establish the degradation pathway and water/sediment distribution pattern of the active substance and its metabolites, breakdown and reaction products. If more than 90% of the active substance is degraded before the period of 100 days expires, the test duration may be shorter.

The degradation pattern of potentially relevant metabolites occurring within the water/sediment study shall be established by extension of the study for the active substance, when it is not possible to extrapolate from point 7.2.2.3 of Part A of these guidelines.

9.3. Fate and behaviour in air

9.3.1. Route and rate of degradation in air and transport via air

If the trigger for volatilisation, Vp = 10^{-5} Pa (for volatilisation from plant) or 10^{-4} Pa (for volatilisation from soil) at a temperature of 20 °C is exceeded and (drift) mitigation measures are required to reduce exposure to non-target organisms, model calculations of off-site deposition (PEC) originating from volatilisation shall be provided. The volatilisation term (PEC) shall be added into the relevant risk assessment procedures for PEC_S and PEC_{SW}. The calculation may be refined using data from confined experiments. Where relevant, laboratory, wind-tunnel or field experiments to determine PEC_S from deposition following volatilisation and mitigation measures shall be provided.

9.4. Estimation of concentrations for other routes of exposure

Suitable estimations (calculations) of predicted environmental concentration, of active substance and metabolites, breakdown and reaction products shall be submitted unless the applicant shows that contamination will not occur in case of exposure by other routes, such as:

— indirect exposure of surface water via a sewage treatment plant (STP) after application of a FPP in storage rooms, and

— amenity use.

PART B: SECTION 10

ECOTOXICOLOGICAL STUDIES

Introduction

1. Testing of the FPP shall be necessary where its toxicity cannot be predicted on the basis of data on the active substance. Where testing is necessary, the aim shall be to demonstrate whether the FPP, taking account of content of active substance, is more toxic than the active substance. Thus bridging studies or a limit test may be sufficient. However, where a FPP is more toxic than the active substance (expressed in comparable units), definitive testing shall be required. Possible effects on organisms/ecosystems shall be investigated, unless the applicant shows that exposure of the organisms or ecosystems does not occur.
Tests and studies conducted using the FPP as test material necessary to assess the toxicity of the active substance shall be reported in the context of the relevant data requirement concerning the active substance.

2. All potentially adverse effects found during routine ecotoxicological investigations shall be reported and such additional studies, which may be necessary to investigate the mechanisms involved and assess the significance of these effects, shall be undertaken and reported.

3. Whenever a study implies the use of different doses, the relationship between dose and adverse effect shall be reported.

4. Where exposure data are necessary to decide whether a study has to be performed, the data obtained in accordance with Section 9 shall be used.
For the estimation of exposure of organisms, all information on the FPP and on the active substance shall be taken into account. A tiered approach shall start with default worst-case parameters for exposure and be followed by a parameter refinement based on the identification of representative organisms. Where relevant, the parameters set out in this Section shall be used. Where it appears from available data that the FPP is more toxic than the active substance, the toxicity data for the FPP shall be used for the calculation of appropriate risk quotients (see point 8 of this introduction).

5. The requirements laid down in this Section shall include certain study types that are set out in Section 8 of Part A of these guidelines. While each point shall be addressed, experimental data

with a FPP shall be generated only if its toxicity cannot be predicted on the basis of data on the active substance. It may be sufficient to test the FPP with that species of a group that was most sensitive with the active substance.

6. A detailed description (specification) of the material used as provided for in accordance with point 1.4 shall be provided.

7. In order to facilitate the assessment of the significance of test results obtained, the same strain of each species shall, where possible, be used in the various toxicity tests specified.

8. The ecotoxicological assessment shall be based on the risk that the proposed FPP poses to non-target organisms. In carrying out a risk assessment, toxicity shall be compared with exposure. The general term for the output from such a comparison is 'risk quotient' (RQ). RQ may be expressed in several ways, for example, toxicity:exposure ratio (TER) and as a hazard quotient (HQ).

9. For those guidelines which allow for study to be designed to determine an effective concentration (EC_X), the study shall be conducted to determine an EC_{10} and EC_{20} along with corresponding 95 % confidence intervals. If an EC_X approach is used, a NOEC shall still be determined.

Existing acceptable studies that have been designed to generate a NOEC shall not be repeated. An assessment of the statistical power of the NOEC derived from those studies shall be carried out.

For solid formulations an assessment of the risk from dust drift on to non-target arthropods and plants shall be required. Details on the likely exposure levels shall be presented in accordance with Section of Part B of these guidelines. For aquatic life, the risk of movement of the whole particle as well as dust particles shall be considered. Until agreed dust dissipation rate assessments are available likely exposure levels shall be used in the risk assessment.

10. Higher tier studies using a FPP shall be designed and data analysed using suitable statistical methods. Full details of the statistical methods shall be reported. Where appropriate, higher tier studies shall be supported by chemical analysis to verify exposure has occurred at an appropriate level.

11. Pending the validation and adoption of new studies and of a new risk assessment scheme, existing protocols shall be used to address the acute and chronic risk to bees, including those on colony survival and devel- opment, and the identification and measurement of sub-lethal effects in the risk assessment.

10.1. Effects on birds and other terrestrial vertebrates

10.1.1. Effects on birds

Possible risks to birds shall be investigated if the toxicity of the FPP cannot be predicted on the basis of the data for the active substance, except, for example, where the FPP is used where birds will experience neither direct nor secondary exposure.
In the case of pellets, granules or treated seeds the amount of active substance in each pellet, granule or seed shall be reported as well as the size, weight and shape of pellets or granules. From that data, the number as well as the weight of pellets, granules or seeds required to achieve the LD_{50} shall be calculated and reported as well.
In the case of baits the concentration of as in the bait (mg active substance/kg) shall be reported.
A risk assessment for birds shall be conducted in accordance with the relevant risk quotient analysis.

10.1.1.1. Acute oral toxicity to birds

Circumstances in which required

The acute oral toxicity of the FPP shall be investigated if toxicity cannot be predicted on the basis of the data for the active substance, or where results from mammalian testing give evidence of higher toxicity of the FPP compared to the active substance, unless the applicant shows that it is not likely that birds are exposed to the FPP itself.

Test conditions

The test shall provide, where possible, LD_{50} values, the lethal threshold dose, time courses of response and recovery, the No Observed Effect Level (NOEL), and shall include gross pathological findings. Study design shall be optimised for the achievement of an accurate LD_{50} rather than for any secondary endpoint.
The study shall be conducted on the species used in the study referred to in point 8.1.1 of Part A of these regulations.
The highest dose used in tests shall not exceed 2 000 mg active substance/kg body weight, however, depending on the expected exposure levels in the field following the intended use of the compound, higher doses may be required.

10.1.1.2. Higher tier data on birds

Higher tier studies on birds shall be conducted where the first tiers of the risk assessment do not demonstrate that risk is acceptable.

10.1.2. Effects on terrestrial vertebrates other than birds

Possible risks to vertebrate species other than birds shall be investigated except when the test substance is included in FPPs used where vertebrate species other than birds will experience neither direct nor secondary exposure.

Experimental testing of vertebrates shall only be carried out where the data required for risk assessment cannot be derived from the data generated in accordance with the requirements set out in Section 5 and 7 of Part A of these regulations.
An acute and reproductive risk assessment for terrestrial vertebrates other than birds shall be conducted in accordance with the relevant risk quotient analysis.

10.1.2.1. Acute oral toxicity to mammals

Circumstances in which required

If exposure to the formulation is considered possible and the toxicity cannot be predicted on the basis of the data for the active substance, data on the acute oral toxicity of the FPP from the mammalian toxicological assessment shall also be considered (see point 5.8 of Part A of these guidelines).

10.1.2.2. Higher tier data on mammals

Higher tier studies on mammals shall be conducted where the first tiers of the risk assessment do not demonstrate that risk is acceptable.

10.1.3. Effects on other terrestrial vertebrate wildlife (reptiles and amphibians)

Where it cannot be predicted from the active substance data and, if relevant, the risk to amphibians and reptiles from FPPs shall be addressed.

Additional long-term and chronic toxicity studies on fish, aquatic invertebrates and sediment dwelling organisms

The studies referred to in points 8.2.2 and 8.2.5 of Part A of these regulations shall be conducted for particular FPPs, where it is not possible to extrapolate from data obtained in the corresponding studies on the active substance (for example the FPP is more acutely toxic than the active substance as manufactured by a factor of 10), unless it is demonstrated that exposure will not occur.

10.1.4. Further testing on aquatic organisms

The studies referred to in point 8.2.8 of Part A of these regulations may be required for particular FPPs where it is not possible to extrapolate from data obtained in the corresponding studies for the active substance or another FPP.

10.2. Effects on arthropods

10.2.1. Effects on bees

The possible effects on bees shall be investigated except where the FPP is for exclusive use in situations where bees are not likely to be exposed.

Testing shall be required if:

— the FPP contains more than one active substance,

— the toxicity of a FPP cannot be reliably predicted to be either the same or lower than the active substance tested, in accordance with the requirements set out in points 8.3.1 and 8.3.2 of Part A of these regulations.

Where bees are likely to be exposed, testing by both acute (oral and contact) and chronic toxicity, including sub-lethal effects, shall be conducted.

Where exposure of bees to residues in nectar, pollen or water resulting from systemic properties of the active substance may occur and where the acute oral toxicity is < 100 μg/bee or a considerable toxicity for larvae occurs, residues concentrations in these matrices shall be provided and the risk assessment shall be based on a comparison of the relevant endpoint with those residue concentrations. If this comparison indicates that an exposure to toxic levels cannot be excluded, effects shall be investigated with higher tier tests.

Acute toxicity to bees

Where bee acute testing with the FPP is required, both acute oral and contact toxicity tests shall be conducted.

10.3.1.1.1. Acute oral toxicity

A test for acute oral toxicity shall be provided establishing the acute LD_{50} values together with the NOEC. Sub-lethal effects, if observed, shall be reported.

Test conditions

Results shall be presented in terms of μg FPP/bee.

10.3.1.1.2. Acute contact toxicity

A test for acute contact toxicity shall be provided establishing the acute LD_{50} values together with the NOEC. Sub-lethal effects, if observed, shall be reported.

Test conditions

Results shall be presented in terms of μg FPP/bee.

10.3.1.2. Chronic toxicity to bees

A test for chronic toxicity to bees shall be provided establishing the chronic oral EC_{10}, EC_{20}, EC_{50} together with the NOEC. Where the chronic oral EC_{10}, EC_{20}, EC_{50} cannot be estimated, an explanation shall be provided. Sub-lethal effects, if observed, shall be reported.

Circumstances in which required

The test shall be carried out where bees are likely to be exposed.

Test conditions

Results shall be presented in terms of μg FPP/bee.

10.3.1.3. Effects on honey bee development and other honey bee life stages

A bee brood study shall be conducted to determine effects on honey bee development and brood activity.
The bee brood test shall provide sufficient information to evaluate possible risks from the FPP on honey bee larvae.
The test shall provide the EC_{10}, EC_{20} and EC_{50} for adult bees/larvae (or an explanation if they cannot be estimated) together with the NOEC. Sub-lethal effects, if observed, shall be reported.

10.3.1.4. Sub-lethal effects

Tests investigating sub-lethal effects, such as behavioural and reproductive effects, on bees and, where applicable, on colonies may be required.

10.3.1.5. Cage and tunnel tests

The test shall provide sufficient information to evaluate:
— possible risks from the FPP for bee survival and behaviour, and
— impact on bees resulting from feeding on contaminated honey dew or flowers.

Sub-lethal effects shall be addressed, if necessary, by carrying out specific tests (for example foraging behaviour).

Circumstances in which required

When acute or chronic effects on colony survival and development cannot be ruled out, further testing shall be required especially if effects are observed in the honeybee brood feeding test (see point 8.3.1.3 of Part A of these guidelines or if there are indications for indirect effects such as delayed action, effects on juvenile stages, or modification of bee behaviour; or other effects such as prolonged residual effects; in those cases cage/tunnel tests shall be carried out and reported.

Test conditions

The test shall be carried out using healthy queen-right honey bee colonies in which pathogens are low and regularly monitored.

10.3.1.6. Field tests with honeybees

The test shall have an adequate statistical power and shall provide sufficient information to evaluate possible risks from the FPP on bee behaviour, colony survival and development.

Sub-lethal effects shall be addressed, if necessary by carrying out specific tests (for example

homing flight).

Circumstances in which required

When acute or chronic effects on colony survival and development cannot be ruled out, further testing shall be required if:
— effects are observed in the honeybee brood feeding test (see point 8.3.1.3 of Part A of these guidelines, or
— there are indications for indirect effects such as delayed action, effects on juvenile stages, or modification of bee behaviour or other effects such as prolonged residual effects.

In those cases field tests shall be carried out.

Test conditions

The test shall be carried out using healthy queen-right honey bee colonies in which pathogens are low and regularly monitored.

10.3. Effects on non-target soil meso- and macrofauna

10.3.1. Earthworms

The possible impact on earthworms shall be reported unless the applicant shows that it is not likely that earthworms are exposed, directly or indirectly.

A risk assessment for earthworm shall be conducted in accordance with the relevant risk quotient analysis.

10.3.1.1. Earthworms — sub-lethal effects

The test shall provide information on the effects on growth and reproduction of the earthworm.

Circumstances in which required

The sub-lethal toxicity of a FPP to earthworms shall be investigated if the relevant criteria as defined in point 8.4.1 of Part A of these guidelines are met, and the toxicity of the FPP cannot be predicted on the basis of the data for the active substance, unless the applicant shows that no exposure occurs.

Test conditions

Testing shall determine a dose-response relationship and the EC_{10}, EC_{20} and NOEC shall enable the risk assessment to be conducted in accordance with the appropriate risk quotient analysis, taking into account likely exposure, the organic carbon content (f_{OC}) of the test medium and the lipophilic properties (K_{OW}) of the test substance. The test substance shall be incorporated into the soil to obtain a homogenous soil concen- tration. Testing with soil metabolites may be avoided if there is analytical evidence to indicate that the metabolite is present at an adequate concentration and duration in the study conducted with the parent active substance.

10.3.1.2. Earthworms — field studies

The test shall provide sufficient data to evaluate effects on earthworms under field conditions.

Circumstances in which required

Where the relevant risk quotient analysis indicates a chronic risk to earthworms a field study to determine effects under practical field conditions shall be conducted and reported as an option for refined risk assessment.

Test conditions

The study design shall reflect the proposed use of the FPP, the environmental conditions likely to arise and species that will be exposed.

If a study is to be used for risk assessment in relation to metabolites, their concentrations occurring shall be confirmed analytically.

10.3.2. Effects on non-target soil meso- and macrofauna (other than earthworms)

Circumstances in which required

Effects on soil organisms (other than earthworms) shall be investigated for all FPPs, except in situations where soil organisms are not exposed.
Testing shall be required if:
— the FPP contains more than one active substance,
— the toxicity of a FPP cannot be reliably predicted to be either the same or lower than the active substance tested in accordance with point 8.4.2 of Part A of these guidelines.

10.3.2.1. Species level testing

The test shall provide sufficient information to perform an assessment of the toxicity of the FPP to the soil invertebrate indicator species *Folsomia candida* and *Hypoaspis aculeifer*.

Test conditions

Testing shall determine a dose-response relationship and the EC_{10}, EC_{20} and NOEC shall enable the risk assessment to be conducted in accordance with the appropriate risk quotient analysis, taking into account likely exposure, the organic carbon content (f_{OC}) of the test medium and the lipophilic properties (Kow) of the active substance in the FPP. The FPP shall be incorporated into the soil to obtain a homogenous soil concentration.

Higher tier testing

The tests shall provide sufficient information to evaluate the risk of the FPP for soil organisms (other than earthworms) using a more realistic test substrate or exposure regime.

Circumstances in which required

Further testing shall be required where significant effects are seen following laboratory testing in accordance with the requirements set out in point 8.4.2.1 of Part A of these guidelines or in accordance with point 10.4.2.1 of this Annexguideline and where risk is indicated following the relevant risk quotient analysis.

Test conditions

Higher-tier tests may take the form of community/population studies (for example. terrestrial model ecosystems, soil mesocosms) or field studies. Timing, levels and routes of exposure shall reflect those of the proposed use of the FPP. Key effect end-points include: changes in community and population structure of both micro and macro-organisms; species diversity; number and biomass of key species/groups.

10.4. Effects on soil nitrogen transformation

The test shall provide sufficient data to evaluate the impact of the FPPs on soil microbial activity

in terms of nitrogen transformation.

Circumstances in which required

The effects of FPPs on soil microbial function shall be investigated if the toxicity of the FPP cannot be predicted on the basis of data for the active substance, unless the applicant shows that no exposure occurs.

10.5. Effects on other terrestrial organisms (flora and fauna)

Any available data on the effects of the FPP on other terrestrial organisms shall be submitted.

10.6. Monitoring data

Available monitoring data concerning effects of the FPP to non-target organisms shall be reported.

PART B: SECTION 11

REFERENCES

References from the scientific peer reviewed open literature on the active substance, metabolites and breakdown or reaction products and FPPs containing the active substance shall be submitted.

PART B: *SECTION 12*

CLASSIFICATION AND LABELLING

Proposals for the classification and labelling of the FPP, where applicable, shall be submitted and justified, including:

— pictograms,

— signal words,

— hazard statements, and

— precautionary statements.