Evaluation Manual for the Authorisation of plant protection products and biocides according to Regulation (EC) No 1107/2009

EU part

Plant protection products

Chapter 7 Ecotoxicology: terrestrial; birds and mammals

version 2.0; January 2014

ctgb

Board for the Authorisation of plant protection products and biocides

Chapter 7 Ecotoxicology; terrestrial; birds and mammals

Category: Plant Protection Products

GENERAL INTRODUCTION

This chapter describes the data requirements for estimation of the effects on birds and mammals of a plant protection product and its active substance and how reference values are derived in the EU framework (§1 - §1.5) Regulation (EC) No 1107/2009 [1].The described risk assessment in this chapter can be used for both the approval procedure for active substances as well as for zonal applications for the authorization of plant protection products (i.e. core registration reports).

Substances that are approved under Regulation (EC) No 1107/2009 and were approved under Directive 91/414/EEC [2] are included in Commission Implementing Regulation (EU) No 540/2011 [3].

The chapter describes the procedures following the data requirements as laid down in Commission Regulation (EU) No 283/2013 for active substances and in Commission Regulation (EU) No 284/2013 for plant protection products. These data requirements apply for active substances submitted after 31 December 2013 and for plant protection products submitted after 31 December 2015.

A concept guidance is available on the interpretation of the transitional measures for the data requirements for chemical active substances according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013 (SANCO/11509/2013 – rev. 0.1).

For further information on the former data requirement as laid down in Commission Regulation (EU) No 544/2011 for active substances and in Commission Regulation (EU) No 545/2011 we refer to the Evaluation Manual for Authorisation of plant protection products according to Regulation (EC) No 1107/2009 version 1.0

1. EU FRAMEWORK

In this document, the procedures for the evaluation and re-evaluation of active substances as laid down in the EU are described; the NL procedure for evaluation of a substance is reverted to when no EU procedure has been laid down. The NL-procedure for the evaluation of a substance is described in §2 - §2.5 of part 2 of the Evaluation Manual (plant protection products). This document aims to give procedures for the approval of active substances and inclusion in Commission Implementing Regulation (EU) No 540/2011 [3].

1.1 Introduction

This chapter describes the risk assessment of plant protection products for birds and mammals. The risk of plant protection products to birds and mammals is evaluated to prevent products that present an unacceptable risk to the environment reaching the market.

The EFSA Guidance Document on Risk Assessment for Birds and Mammals [4] is used for the evaluation, at least for all dossiers submitted to the Netherlands since 13/07/2012. Data requirements, evaluation methodologies, criteria and trigger values that deviate from, or further elaborate, the provisions under EU framework (§1), are described under NL framework (§2 - §2.5). The national further provisions can also be used for inclusion of an active substance in Commission Implementing Regulation (EU) No 541/2011.

1.2 Data requirements

In order to qualify for inclusion of an active substance in Commission Implementing Regulation (EU) No 540/2011 [3] a dossier that meets the provisions laid down in Commission Regulation (EU) No 283/2013 [5] and Commission Regulation (EU) No

284/2013 of Regulation (EC) No 1107/2009 [6] must be submitted for the active substance as well as for the product.

Generally, EU and OECD guidelines for the protocol of experiments are mentioned in Commission Communication 2013/C 95/01 [7].

It is therefore strongly recommended to consult the guidance documents as well; the guidance documents are applicable where differences exist.

When according to the applicant a certain study is not necessary, a relevant scientific justification can be provided for the non-submission of the particular study.

The data requirements, and the fact whether or not they are required for certain fields of use, and the corresponding guidelines are summarised in the overview table; see Appendix A to Chapter 7.

1.2.1 Data requirements for the active substance

The text below in grey frames has been taken from Commission Regulation (EU) No 283/2013. The numbering in these grey frames follows the section numbering in this Commission Regulation. Any necessary additions to the text have been added below the grey frames. Question numbers (NL as well as EU) are given below the headings.
The endpoints of the study are given as well, if relevant.

The data requirements regarding the risk of the active substance to birds and mammals are described in Commission Regulation (EU) No 283/2013, point 8.1 (effects on birds and other terrestrial vertebrates).

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 plant protection 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 plant protection 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 plant protection product types (for example encapsulated suspension) testing with the plant protection product is more appropriate to testing with active substance when these organisms will be exposed to the plant protection product itself. For plant protection 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, plant protection 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). The methodology for derivation of these endpoints is outlined in the 'Technical Guidance for Deriving Environmental Quality Standards([1])' for the Water Framework Directive 2000/60/EC of the European Parliament and of the Council ([2]).

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 development, and the identification and measurement of relevant sub-lethal effects in the risk assessment.

Effect on birds and other terrestrial vertebrates
(283/2013; 8.1)

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.

Effects on birds
(283/2013; 8.1.1)

Acute oral toxicity to birds
(283/2013; 8.1.1.1)

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 plant protection products used, for example, in enclosed spaces and wound healing treatments 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.

Result acute oral toxicity:
→ LD_{50} expressed in mg/kg mg/kg bw.

Short-term dietary toxicity to birds
(283/2013 ; 8.1.1.2)

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.

Result dietary study:
→ LC_{50} expressed in mg/kg bw/d.

Sub-chronic toxicity and reproduction toxicity to birds
(283/2013 ; 8.1.1.3)

8.1.1.3. Subchronic toxicity and reproduction 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.
Test guideline
The test must be carried out in accordance with OECD Method 206 [8].

*Additional note Ctgb: the latter argument is under discussion and considered not true by some member states, including the Netherlands. Exposure outside the breeding season can still lead to effects during breeding seasons. Especially in cases of substances which are expected to have endocrine disruption effects. Thus only the argument that application is outside the breeding season is not considered enough to disregard long-term risk assessment.

Result subchronic and reproduction toxicity:
→ NOEC (based on concentration in food, in mg/kg food), should be converted to an NOAEL (based on daily dose, in mg/kg bw/d). Where no data are known about food intake and/or body weight, default conversion factors can be used. See the Guidance document on birds and mammals (2009,section 2.3.1.1).[4]

Effects on terrestrial vertebrates other than birds
(283/2013; 8.1.2.)

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.

Acute oral toxicity to mammals
(283/2103; 8.1.2.1.)

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 plant protection products used, for example, in enclosed spaces and wound healing treatments where mammals will experience neither direct nor secondary exposure.

Long-term and reproductive toxicity to mammals
(283/2103; 8.1.2.2.)

8.1.2.1 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.

Active substance bioconcentration in prey of birds and mammals
(283/2013; 8.1.3.)

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.

Effects on terrestrial vertebrate wildlife (birds, mammals, reptiles and amphibians)
(283/2013; 8.1.4.)

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.

Endocrine disrupting properties
(283/2013; 8.1.5)

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.

1.2.2 Data requirements for the product

The text below in grey frames has been taken from Commission Regulation (EU) No 284/2013. The numbering in these grey frames follows the section numbering in this Commission Regulation. Any necessary additions to the text have been added below the grey frames. Question numbers (NL as well as EU) are given below the headings.
The endpoints of the study are given as well, if relevant..

The data requirements regarding the risk of the plant protection product to birds and mammals are described in Commission Regulation (EU) No 284/2013, point 10.1 (effects on birds and other terrestrial vertebrates).

Generally, EU and OECD guidelines for the protocol of experiments are mentioned in Commission Communication 2013/C 95/02 [9].

Introduction

1. Testing of the plant protection product 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 plant protection product, 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 plant protection product 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 plant protection product 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 plant protection product 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 plant protection product is more toxic than the active substance, the toxicity data for the plant protection product 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 the Annex to Regulation (EU) No 283/2013 (such as standard laboratory tests with birds, aquatic organisms, bees, arthropods, earthworms, soil micro-organisms, soil meso-fauna and non-target plants). While each point shall be addressed, experimental data with a plant protection product 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 plant protection product 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 plant protection 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’ (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.

10. 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 9 of this Annex. 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.

11. Higher tier studies using a plant protection product 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.

12. 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 development, and the identification and measurement of sub-lethal effects in the risk assessment.

Effects on birds and other terrestrial vertebrates
(284/2103; 10.1)

Effects on birds
(284/2103; 10.1.1.)

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 plant protection product cannot be predicted on the basis of the data for the active substance, except, for example, where the plant protection product is used in enclosed spaces or for wound-healing treatments 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 (1) 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.

Acute oral toxicity to birds
(284/2013 ; 10.1.1.1)

10.1.1.1. Acute oral toxicity to birds

Circumstances in which required
The acute oral toxicity of the plant protection product 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 plant protection product compared to the active substance, unless the applicant shows that it is not likely that birds are exposed to the plant protection product 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 the Annex to Regulation (EU) No 283/2013.

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.

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Result:
→ LD_{50}

Higher tier data on birds
(284/2013; 10.1.1.2.)

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.

Effects on terrestrial vertebrates other than birds
(284/2013; 10.1.2)

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 plant protection products used, for example, in enclosed spaces and wound-healing treatments 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 the Annex to Regulation (EU) No 283/2013.

An acute and reproductive risk assessment for terrestrial vertebrates other than birds shall be conducted in accordance with the relevant risk quotient analysis.

Acute oral toxicity to mammals
(284/2013; 10.1.2.1.)

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 plant protection product from the mammalian toxicological assessment shall also be considered (see point 5.8 of Part A of the Annex to Regulation (EU) No 283/2013).

Higher tier data on mammals
(284/2013; 10.1.2.2.)

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.

1.2.3 Data requirements for metabolites

Data requirements for metabolites are not clearly reported for the section ecotoxicology.

The only reference in Commission Regulation (EU) No 283/2013 and Commission Regulation (EU) No 284/2013 for ecotoxicology is:

'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.'

Separate guidance documents have included a more detailed sections on metabolites. More detailed information on datarequirements for metabolites is given below, taken from different guidance documents.

~~The data requirements have not yet been brought in line with the latest versions of the different guidance documents (see 1.2). Data requirements for metabolites have not yet been included in Commission Regulation (EU) No 283/2013 and Commission Regulation (EU) No 284/2013. For reasons of clarity, the data requirements applying for metabolites are, ahead of the amendment of Commission Regulation (EU) No 283/2013 and Commission Regulation (EU) No 284/2013, described below.~~

1.2.3.1 Metabolites - terrestrial ecotoxicology
As a general principle it should be kept in mind that data requirements for metabolites mentioned in this section do not always need to be met by means of experimental studies. Applicants may also answer the open questions by means of other available information in support of a scientific and rational risk assessment.

Valuable sources of information are e.g.:
- the molecular structure of the metabolite (is the active part still intact?);
- the presence of metabolites in existing tests with the active substance and/or major metabolites ($\geq$ 10%);
- general knowledge about the relationship between the toxicity of metabolites and the active substances from which these are formed;
- information about the pesticidal activity from biological screening data;
- available knowledge about substances that are related to the metabolites.

No further studies are required where a metabolite is CO_2 or an inorganic substance, not being or containing a heavy metal, or an organic substance with an aliphatic structure, with a chain length of 4 or less, which only consists of C, H, N or O atoms and contains no "structures" or functional groups that are known as ecotoxicologically relevant.
The metabolite is in such cases considered as ecotoxicologically not relevant and has a low risk to the environment.
Generally, a risk assessment is required for all metabolites. Minor metabolites (<10%), however, only need consideration in exceptional cases, e.g. if containing the active moiety of the molecule. By definition the PEC for a minor metabolite is lower than the PEC for the parent compound by more than a factor of 10; accordingly minor metabolites even if up to 10 times as toxic as their parent compound can be considered as safe, provided that the parent compound is safe and also provided that no new concern with regard to persistence is brought in.

Where metabolites are identified in laboratory studies but not in field studies, the field studies must be considered as most relevant unless the difference is caused by the

methods used.
Tests with metabolites may not be required in case they are formed relatively rapidly and are present for a short time because they may in such cases have been taken into account in the toxicity tests with the active substance. Such conclusions must, however, be supported by analytical measurements.
Where more than one metabolite is considered as significant, it may be sufficient to conduct tests only with the most important metabolite (highest formation percentage, structure most comparable to the active substance).
Where higher tier studies have been carried out with the active substance, or a relevant formulation, the metabolites may have been taken into account in these studies (depending on the duration of the study and the degradation behaviour of active substance and metabolites).
In principle, the risk assessment for metabolites is the same as for the active substance. In case the metabolite is less toxic than the active substance, it will in most cases entail no greater risk than the active substance, which means that a detailed quantified risk assessment is not required. Exceptions are those metabolites that are more persistent and show more bioaccumulation than the active substance, which may result in differences in long-term exposure.

1.2.3.2 Metabolites - birds and mammals
In the EFSA Guidance Document for risk assessment on birds and mammals [4] a separate section on how the deal with metabolites can be found. In general, metabolites should be taken into account but that additional testing on birds or mammals should be prevented a much as possible. See for further information EFSA 2009, section 5.4.

1.3 Risk assessment

The risk assessment methodology for birds and mammals has in EU context been elaborated in the EFSA Guidance Document on Risk Assessment for Birds and Mammals [4].

Each study is summarised and analysed separately. The final conclusion and the endpoint per aspect (such as LD_{50}) are presented in a list of endpoints.
Risk assessment is based on comparison with endpoints.

1.3.1 Further elaboration on the risk assessment

As the guidance document is relatively new (prepared in December 2009, into force in July 2012) an evaluation round is scheduled for the second part of 2012. However, this has not been done so far. The Netherland has sent in comments on the original document, for which either more information or revision should take place. In the section below is listed on which points the Netherlands does not agree with the current version of the guidance document and for which a different view is used in European risk assessment.
Additionally, some points from the guidance document especially in the refinements options are not worked out completely. Choices are left to the risk manager / evaluator. For some points the Netherlands has made choices for these refinements. These points are also reported below.

Higher tier refinements
- As stated in the EFSA 2009 guidance [4], Extrapolation of study results from one MS or zone to another (section 6.1.3.2) should be done with care.
When using field studies it should be clear that the circumstances in which the study was performed are comparable to the Dutch situation. Therefore an argumentation should be presented when extrapolating from studies performed in <u>other</u> countries than the following:

Belgium
Denmark
Germany
Ireland
Luxembourg
Northern France
The Netherlands
The United Kingdom

- For the refinement on DT_{50} used in MAF-calculation and F_{twa} calculation, the geometric mean is preferred, which is in line with FOCUS kinetics.

-When using refined mean RUD values, the worst-case of either the geometric or the arithmetic mean should be used.

- The 90%-tile PT should be used (as discussed in PRAPeR 80). This is based on the following considerations;

- Due to uncertainties in deriving PT values (sample size, representativeness of study location, etc) proposed that 90th%ile value should be used. Alternative view that in some cases the mean PT value may be appropriate e.g. depending on sensitivity of focal species.
- PT is measured over short-term on multiple birds to extrapolate to likely behaviours of individuals over long-term to protect the population using the field.
- Uncertainty in extrapolating from results from one study in one location to other areas of Europe.
- Historically, 90th%ile PT values have been used, especially in cases where crops differ to proposed use.

Additionally, the worst-case maximum PT value from field study is used when <10 individuals tracked; when ≥10 individuals tracked use 90th%ile PT value.

Seed treatments/granules/potatoes (tubers), flowerbulbs (dipping)
- in the granule risk assessment for birds (section 5.1.3) a daily grit dose is calculated (DGritD) expressed in dose/ bird/day. As the LD50 or NOEAL are expressed in mg/kg bw/d a correction for body weight of the target species should be performed. This is a known flaw in the EFSA guidance and will corrected in the following update.

- a refinement of the risk evaluation for treated seed is possible by taking the percentage of treated seed that remains at the surface into account. The largest part of the seed is incorporated into the soil and is therefore not accessible for birds and mammals (the digging up of seeds is not taken into consideration because data about this are lacking). As starting point it is assumed that 0.5% of the seeds remains at the surface in case of precision drilling. For standard drilling it is assumed for spring application that 3.3% of the seeds remain at the surface; this percentage is 9.2% in case of autumn application.
The following crops have been studied: onion, sugar beet, maize, alfalfa, flax, pea, spring wheat and winter wheat [10]. It should be determined via expert judgement to which extent other crops are comparable.

-no guidance is given for risk assessment for treated potato tubers. In recent risk assessments, several focal species were proposed:

<u>Birds</u>

The common crane *(Grus grus)* is not a common species in the Netherlands, but it does visit and forage in (parts of) the country when passing it on their migratory route in spring (Mar-Apr) and wintertime (Oct-Dec). For the common crane, a body weight of 5371 g and a daily food intake of 380 g/day are given in addendum 1 to the DAR of flutolanil (October 2006). FIR/bw is 0.071. This value can be used in risk assessment for common crane. Geese are also know to eat potatoes. However, this normally occurs in wintertime (just before harvest), and not in springtime when treated potatoes will be sown. In conclusion, the common crane is considered to be a reasonable focal species for the Netherlands to indicate possible risks to birds.

Mammals

Large mammal species that might feed on potatoes in the Netherlands are the badger *(Meles meles)* (as used in the EU assessment of flutolanil) and the wild boar *(Sus scrofa)* (used in the EU risk assessment of pencycuron and penflufen). After consultation with a badger expert from the Dutch Mammal Association the badger is not considered to be a relevant species for this use, at least not in the Netherlands. Although a badger might incidentally try a potato, potatoes are not a normal part of the badger diet. The wild boar is more relevant.
For the wild boar, the mean daily food intake rate is estimated at 4 kg fresh material and the body weight of adult males and females amounts to 104 and 84 kg, respectively (DAR pencycuron, October 2005). FIR/bw is 0.05. In the DAR of penflufen the same data is used, however also a young boar of 25 kg is considered, with a consumption rate of 5 kg. However, this is considered to be an translation error, the consumption rate for young boars reported is 2.5 kg (FIR/bw is 0.1). Since young animals are usually not used as basis of the Fir/bw, it is considered to use the reported highest consumption rate female boars (7 kg), which leads to a FIR/bw of 0.08 as a reasonable worst-case.

-degradation/dissipation in seedlings. In the guidance it is stated that the appropriate time window and default degradation and dissipation rates for residues should be considered in the risk assessment via consumption of newly emerged crop shoot. However, the default DT50 of 10 days is only considered valid for surfaces (on leaves and seeds), exposed to weathering. Thus the default DT50 is not automatically considered valid for concentration decline in seedings bulbs etc..

Bioconcentration in earthworms
-For persistent substances, TER calculation should be performed with the $PEC_{plateau}$ + PEC_{21d}.
-Pore water approach is not used since there is no agreed calculation for the PEC porewater

'Pre-emergence' uses.
For pre-emergence uses it is often argued that exposure via plants (weeds, grasses) is not relevant. However, the pre-emergence is usually the stage of the crops of concern, not the stage of the weeds and grasses. The exclusion of the foliar part in the diet can therefore only be used when it is also evident that weeds and grasses are absent at the time of application (for instance, application, directly after tillage). Also for systemic substances, the foliar part of the diet cannot be excluded. Thus for pre-emergence applications, the following additions should be made to the EFSA guidance:

	Presence of weeds and grasses can be excluded (application	**Presence of weeds and grasses cannot be excluded**

	directly after seeding or planting)	
Systemic	Use the scenarios identified for the next crop stages (BBCH 10-19) to include relevant foliage part of the diet. Use the data for sprayed exposure to foliage, unless measured data of concentrations after systemic exposure in plants is available.	Use the scenarios identified for the next crop stages (BBCH 10-19) to include relevant foliage part of the diet. Use the data for sprayed exposure to foliage, unless measured data of concentrations after systemic exposure in plants is available.
Non-systemic	Foliage is not relevant, bare soil scenario can be used.	Use the scenarios identified for the next crop stages (BBCH 10-19) to include relevant foliage part of the diet.

Combination toxicity
The assessment how to deal with combined effects is described in Appendix B from the Guidance document [4]. For the sublethal effects and the effects on reproduction, calculation of combined toxicity is not recommended, because this could be biased by using different effects (effects on parent vs effects on offspring) by the choice of dose spacing. Therefore it is recommended to perform a risk assessment on a case-by case basis. Ctgb is aware of these short-comings when taking into account risk assessment but is of the opinion that the combined effects should not be easily disregarded. Thus a risk assessment based on concentration addition should be performed, unless it is made clear in a statement that this is not relevant.

1.4 Approval

This section describes the approval criteria for active substances (section 1.4.1) and plant protection products (section 1.4.2 and 1.4.3). For the EU approval procedure of active substances a representative formulation has to be included in the dossier. Therefore section 1.4.1 to 1.4.3 apply. For the zonal applications of plant protection products only section 1.4.2 and 1.4.3 apply.

1.4.1 Approval of the active substance

Regulation (EC) No 1107/2009 Annex II provides the procedure and criteria for the approval of an active substances, safeners and synergists pursuant to Chapter II of Regulation (EC) No 1107/2009.

Point 3 of Annex II of Regulation (EC) No 1107/2009 gives the criteria for the approval of an active substance. The texts specifically applicable to the aspect birds and mammals are presented below.

3. Criteria for the approval of an active substance

3.1. Dossier

The dossier submitted pursuant to Article 7(1) shall be sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.

3.3. Relevance of metabolites
Where applicable the documentation submitted shall be sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.

3.8. Ecotoxicology
3.8.1. An active substance, safener or synergist shall only be approved if the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The assessment must take into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.
3.8.2. An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines, it is not considered to have endocrine disrupting properties that may cause adverse effects on non-target organisms unless the exposure of non-target organisms to that active substance in a plant protection product under realistic proposed conditions of use is negligible.

1.4.2 Evaluation of plant protection products

The principles for evaluation of the effects on the environment are presented in Commission Regulation (EU) No 546/2011 [11]. These are the relevant sections of the introductory principles, the general principles and the specific principles Environmental effects.
The specific principles Environmental effects, part Effect on species that are no target species are, as regards birds and mammals, in the text below printed in a grey frame. This text, including numbering, is the literal text from Commission Regulation (EU) No 546/2011.

2.5.2.1. Member States shall evaluate the possibility of exposure of birds and other terrestrial vertebrates to the plant protection product under the proposed conditions of use; if this possibility exists they shall evaluate the extent of the short-term and long-term risk to be expected for these organisms, including their reproduction, after use of the plant protection product according to the proposed conditions of use.
(a) This evaluation will take into consideration the following information:
(i) the specific information relating to toxicological studies on mammals and to the effects on birds and other non-target terrestrial vertebrates, including effects on reproduction, and other relevant information concerning the active substance as provided for in the Annex to Regulation (EU) No 544/2011 and the results of the evaluation thereof;
(ii) all relevant information on the plant protection product as provided for in the Annex to Regulation (EU) No 545/2011, including the information on effects on birds and other non-target terrestrial vertebrates;
(iii) where relevant, other authorized uses of plant protection products in the area of envisaged use containing the same active substance or which give rise to the same residues;
(b) This evaluation will include:
(i) the fate and distribution, including persistence and bioconcentration, of the active substance and of relevant metabolites, breakdown and reaction products in the various parts of the environment after application of the plant protection product;

(ii) the estimated exposure of the species likely to be exposed at the time of application or during the period that residues are present, taking into account all relevant routes of exposure such as ingestion of the formulated product or treated food, predation on invertebrates, feeding on vertebrate prey, contact by overspraying or with treated vegetation;
(iii) a calculation of the acute, short-term and, where necessary, long-term toxicity/exposure ratio. The toxicity/exposure ratios are defined as respectively the quotient of LD50, LC50 or non-observable effects of concentration (NOEC) expressed on an active substance basis and the estimated exposure expressed in mg/kg body weight.

1.4.2 Decision making for plant protection products

The principles for decision making as regards the effects on the environment are presented in Commission Regulation (EU) No 546/2011. These are the relevant sections of the introductory principles, the general principles and the specific principles Environmental effects.
The specific principles Environmental effects, part Effect on species that are no target species are, as regards birds and mammals, in the text below printed in a grey frame. This text, including numbering, is the literal text from Commission Regulation (EU) No 546/2011.

2.5.2.1. Where there is a possibility of birds and other non-target terrestrial vertebrates being exposed, no authorisation shall be granted if:
- the acute and short-term toxicity/exposure ratio for birds and other non-target terrestrial vertebrates is less than 10 on the basis of LD50 or the long-term toxicity/exposure ratio is less than 5, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact occurs after use of the plant protection product according to the proposed conditions of use;
- the bioconcentration factor (BCF, related to fat tissue) is greater than 1, unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable effects occur - directly or indirectly - after use of the plant protection product according to the proposed conditions of use.

Note: the BCF in this case should actually be the BAF (bioaccumulation factor)

1.5. Developments

- The EFSA guidance document should have had an evaluation round in 2012. However this is postponed. Up to now, it is not clear when this evaluation round will take place.
- A spread-sheet for quick calculations is available at the EFSA website. However, it is known that the calculator tool still contains mistakes.

2 APPENDICES

None

3 REFERENCES

1 Regulation (EC) No 1107/2009, http://eur-lex.europa.eu/Notice.do?checktexts=checkbox&val=504604%3Acs&pos=1&page=1&lang=en&pgs=10&nbl=1&list=504604%3Acs%2C&hwords=&action=GO&visu=%23texte

2 Directive 91/414/EEC, http://eur-lex.europa.eu/Notice.do?checktexts=checkbox&val=172911%3Acs&pos=3&page=1&lang=en&pgs=10&nbl=3&list=447073%3Acs%2C185439%3Acs%2C172911%3Acs%2C&hwords=&action=GO&visu=%23texte

3 Commission Implementing Regulation (EU) No 540/2011, http://eur-lex.europa.eu/Notice.do?checktexts=checkbox&val=574460%3Acs&pos=6&page=1&lang=en&pgs=10&nbl=6&list=646199%3Acs%2C628324%3Acs%2C615541%3Acs%2C607847%3Acs%2C607130%3Acs%2C574460%3Acs%2C&hwords=&action=GO&visu=%23texte

4 EFSA Journal 2009; 7(12):1483; On request from EFSA, Question No EFSA-Q-2009-00223

5 Commission Regulation (EU) No 283/2013, http://eur-lex.europa.eu/Notice.do?val=724582:cs&lang=en&list=729945:cs,724582:cs,&pos=2&page=1&nbl=2&pgs=10&hwords

6 Commission Regulation (EU) No 284/2013, http://eur-lex.europa.eu/Notice.do?val=724566:cs&lang=en&list=729902:cs,724566:cs,&pos=2&page=1&nbl=2&pgs=10&hwords=

7 Commission Communication 2013/C 95/01 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:095:0001:0020:EN:PDF

8 OECD 206 Avian Reproduction Test (adopted 4 April 1984)

9 Commission Communication 2013/C 95/02 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:095:0021:0037:EN:PDF

10 De Snoo, G.R. en R. Luttik (2004). Availability of pesticide-treated seed on arable fields. Pest Management Science 60:501-506.

11 Commission Regulation (EU) No 546/2011, http://eur-lex.europa.eu/Notice.do?checktexts=checkbox&val=574598%3Acs&pos=2&page=1&lang=en&pgs=10&nbl=2&list=607713%3Acs%2C574598%3Acs%2C&hwords=&action=GO&visu=%23texte