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

NL part

Plant protection products

Chapter 3 Analytical Methods

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Board
for the authorisation
of Plant protection products and Biocides

Chapter 3 Analytical methods

Category: Plant protection products

GENERAL INTRODUCTION

This chapter describes the data requirements for the aspect analytical methods and how these are evaluated for the NL framework (§2 - §2.5).

Substances that are approved under Regulation (EC) No 1107/2009 [1] 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.

2. NL FRAMEWORK

The NL framework (§2 - §2.5) describes the authorisation procedure for plant protection products based on existing substances included in Commission Implementing Regulation (EU) No 540/2011 [3], and new active substances.
A new substance is a substance not authorised in any of the Member States of the EU on 25th of July 1993.
The plant protection product that contains such active substances may be authorised if the approval criteria laid down in Regulation (EC) No 1107/2009 [1] are met, also taking into account the national stipulations described in the Bgb (Plant protection products and Biocides Decree) [4]. The evaluation dossiers must meet the requirements in Commission Regulation (EU) No 283/2013 [5] and Commission Regulation (EU) 284/2013 [6] implementing Regulation (EC) No 1107/2009 [1] (see Application Form and corresponding instructions).

A Member State may deviate from the EU evaluation on the basis of agricultural, phytosanitary and ecological, including climatological, conditions which are specific for the Netherlands.

The NL framework describes the data requirements (§2.2), evaluation methodologies (§2.3), criteria and trigger values (§2.4) for which specific rules apply in the national approval framework or where the national framework has been elaborated in more detail than the EU framework.

The NL procedure described in §2 - §2.5 of this chapter can also be used for evaluation of a substance for approval, and consequently inclusion in Commission Implementing Regulation (EU) No 540/2011 [3] where no EU procedure has been described.

2.1. Introduction

The aspect analytical methods has a specific data requirement regarding water that deviates from those described in the EU framework.

The NL procedure is only described if no EU procedure has been described.

2.2. Data requirements

The data requirements for chemical active substances and plant protection products are in agreement with the provisions in EU framework (see §1.2 of this chapter). Further clarification of the EU data requirements is given in the text below.

The studies must be carried out in compliance with the applicable guidelines. A review of the guidelines and whether or not these are required for particular fields of use for pre- and post-registration methods in technical material and formulations (NL framework) is given in Appendix 3 of this chapter.

For an overview of pre- and post-registration methods (NL framework) reference is made to Appendix 4 to this chapter.

No GLP is required for validation of the analytical methods. Experiments carried out after 25th of July 1993 and which use these analytical methods must, however, be carried out under GLP.

2.2.1 Validation in groundwater and surface water

The Dutch situation for pre-registration analytical methods is the same as the European situation.

For post-registration the Dutch situation is important for the analytical method in surface water. A lot of surface water and groundwater is used for drinking water production, about two thirds of the drinking water is produced from groundwater.

Further to a decision of the College van Beroep voor het bedrijfsleven (CBb; Court of Appeal on Trade and Industry) of 19 August 2005 (AWB 04/37) approval should be judged against the drinking water criterion. The criterion set for surface water intended for drinking water production is that the concentration of any pesticide and its metabolites must be lower than 0.1 µg/l. The Ministries have indicated that they adopt this line and an evaluation method is currently being developed with great urgency. As long as no definitive evaluation method is available, the Board will apply the procedure described in C-163.5 (see Appendix 3, Chapter 6 Behaviour and fate in the environment; behaviour in surface water, sediment and sewage treatment plants (RWZI)).

According to Directive 98/83/EEC [7] it must be possible to check drinking water and water that is used for the production of drinking water for (*inter alia*) pesticides, where a limit of 0,1 µg/l is applied for the concentration of pesticides. Furthermore, the measured pesticides concentration in groundwater may not exceed 0.1 µg/l, or otherwise as laid down in Commission Regulation (EU) 546/2011 [8]. This means that determination of pesticides in groundwater as well as in surface water must be possible at a level of 0.1 µg/l. One of the criteria to be met by a concentration measurement in the environment is that the analysis takes place with at least two independent analytical methods, which are substance-specific as well; a mass selective detector in one of the analytical methods is preferred. In addition, the composition of much surface water in the Netherlands differs from average European water. In particular, the organic matter concentration is much higher. It must also be possible, however, to analyse such waters for monitoring pesticides behaviour.
The EU criterion for the concentration required to establish the limit of quantification for surface water depends on the target species and can be derived from toxicity tests (LC_{50}, NOEC or EC_{50}) SANCO/825/00 “Guidance document on residue-analytical methods”. According to the EU criterion, it applies for groundwater that it must still be possible to measure the lowest concentration given below (See chapter 6 Behaviour and fate in the environment, behaviour in soil: leaching (plant protection)):

(i) the maximum permissible concentration laid down by Directive 2006/118/EC of the European Parliament and of the Council[1]; or
(ii) the maximum concentration laid down when approving the active substance in accordance with Regulation (EC) No 1107/2009, on the basis of appropriate data, in particular toxicological data, or, where that concentration has not been laid down, the

1 OJ L 372, 27.12.2006, p. 19.

concentration corresponding to one tenth of the ADI laid down when the active substance was approved in accordance with Regulation (EC) No 1107/2009, unless it is scientifically demonstrated that under relevant field conditions the lower concentration is not exceeded.

All this has led to the requirement that in the Netherlands the maximum limit of quantification (LOQ) for groundwater and surface water must be 0.1 µg/L unless it must according the European criteria be possible to measure a lower concentration.
The maximum limit of quantification will in that case have to be equal to this lower value.

2.2.2 Confirmatory method for post registration

SANCO/825/00 rev 8.1 does not clearly indicate how a confirmatory method must be evaluated and to which validation it must be subjected. In the Netherlands the following minimal requirements have been laid down for the confirmatory method:

Subject	*Requirement*
The confirmatory method should at the most have the same LOQ as the original method	Five times a measurement in the matrix concerned at LOQ level
The confirmatory method should have a clearly different selectivity than the original method (example: an HPLC separation with a C8 or a C18 column will hardly ever give sufficient difference in selectivity)	For each matrix* a chromatogram per method from which the difference in selectivity can be read. In case one of the methods is not based on chromatography, the difference in selectivity should be described
No confirmatory method is required if the method as such is sufficiently selective as result of the use of mass selective detection	The choice of the mass fragments should be explained, if applicable provided with a mass selective chromatogram in blank as well as in matrix

*) See SANCO/825/00 rev 8.1. In case of plant matrices, data on only one crop need to be submitted if several crops in the application belong to 1 representative crop group (see §2.3.1).

The quality of the confirmatory method can, e.g., be determined by comparison with the results of the original method. In case one and the same sample are analysed with the original method (om) and the confirmatory method (cm), the ratio between the results (C_{bm}/C_{om}) should be between 0.8 and 1.2.

2.2.3 Validation new formulation type

For the validation of new formulation types, the following elaboration of the EU requirements has been agreed bilaterally with Germany:
Where an analytical method for determination of the active substance in a plant protection product has already been validated for a different formulation type than the requested plant protection product, validation of the analytical method for the requested plant protection product can be restricted to: specificity (including blanks), accuracy (recovery; n ≥ 2), precision (repeatability; n ≥ 3). This means that renewed determination of the linearity is not required provided that the concentration of the active substance of the requested plant protection product falls within the range of the method.

2.2.4 Reporting

A number of important aspects regarding the reporting of the analytical methods (validation) is described below, as elaboration of the data requirements laid down in EU framework (see §1.2). The following should at least be included in the description of the method (validation):

- the way in which the (standard) addition has been carried out and at which moment of the procedure
- full repetition of the calculations must be possible with the data in the methods
- individual measurements should be given, not only the averages

- purity and storage date of the standards used
- where applicable, data about the storage method of the sample
- if outliers are observed, e.g. with Dixons test, these may only be excluded from the calculations in case of an acceptable explanation

2.3. Evaluation methodology

The evaluation methodologies for Plant protection products comply with the description under EU framework (see §1.3 of the EU part of the Evaluation Manual for PPP).
Further elaborations of the EU procedure are presented in the text below.

2.3.1 Classification into crop groups

SANCO/825/00 is used to determine to which groups certain crops belong. In case the EU guidance document is not clear, a report prepared by RIVM is used in which it is for all crops indicated to which category they belong [9]. This document is not a new approach but attempts to clarify the different group and category classifications.
The following 4 crop types are distinguished: water/fat/dry and acid. The last group (acid) includes the citrus fruits but these can also be classified as aqueous crops when the correct pH is used during extraction.

2.4. Approval

The evaluation of Plant protection products on the basis of existing active substances already included in Commission Implementing Regulation (EU) No 540/2011 [3] and or new substances has been laid down in Regulation (EC) No 1107/2009 [1]. Where no European methodology is agreed upon, a national methodology is applied as described in the Plant protection product and Biocides Decree (Bgb) [4].

2.4.1 Criteria and trigger values

The criteria and trigger values are in compliance with the European regulations, see §1.4 of the EU part of the Evaluation Manual PPP.

2.4.2 Decision making

Decisions on approval are taken in compliance with the European regulations, see §1.4 of the EU part of the Evaluation Manual PPP.

2.5. Developments

The nVWA (Food and Consumer Product Safety Authority) is currently developing a multiresidue method with LC/MS instead of GC/MS. This will be published after validation.

3. APPENDICES

For Requirements regarding the active substance, Requirements regarding the plant protection product and the List of Endpoints (LOEP) see the EU part of the evaluation manual, appendix 1,2 and 5.

Appendix 1 Summary of the most important requirements for methods in technical material and formulations (NL framework)

Required	Technical a.s.	Formulations
Description of the method	Complete description required	Complete description required
Analytical method based on generally available laboratory equipment and laboratory facilities	Not required, but the necessity must be explained when used	Not required, but the necessity must be explained when used
Avoid dangerous chemicals	Not required, but the necessity must be explained when used	Not required, but the necessity must be explained when used
Derivatisation	Permitted, but the necessity must be explained when used; supplementary validation	Permitted, but the necessity must be explained when used; supplementary validation
Multi Residue Method	Not required	Not required
Validation report in each matrix	Only for the technical material	For each formulation type
Validation report for compounds	- Active substance - Significant impurities - Relevant impurities	- Active substance - Relevant impurities
Confirmatory method	Required when proposed method is not specific	Required for relevant impurities when the proposed method is not specific
Independent laboratory validation (ILV)	Not required	Not required
Limit Of Quantification (LOQ)	a.s.: not required impurities: required, 0.1% w/w for significant and specification level for relevant impurities	a.s.: not required impurities: required for relevant impurities
Range of the method	a.s.: from lowest to highest concentration (+/- 20%) in technical material impurities: from 0.1% w/w (or specification for relevant impurities) to highest concentration (+/- 20%) in technical material.	a.s.: from lowest to highest concentration (+/- 20%) in technical material. impurities: for relevant impurities from specification to highest concentration (+/- 20%) in technical material
Calibration model (linearity or other)	Required Preferably expressed in mg/kg technical a.s. Based on 5 concentration levels or based on 3 duplicate concentration levels Correlation coefficient ≥ 0.99	Required Preferably expressed in mg/kg technical a.s. Based on 5 concentration levels or based on 3 duplicate concentration levels Correlation coefficient ≥ 0.99
Interference of matrix	maximum 3%	maximum 3%

Specificity and identity	Required, it must be possible to determine isomers separately, identity can be determined once	Required, it must be possible to determine isomers separately, in case more active substances are present, it must be possible to analyse these separately
Accuracy / average recovery	a.s.: not required impurities: required (n ≥ 2) at level in relation to specification 70-110 %	a.s.: required (n ≥ 2) at level of formulations impurities: required for relevant impurities (n ≥ 2) See §1.3.1 for requirements
Repeatability (relative standard deviation)	Required, (n ≥ 5), should meet Horwitz, see §1.3.1	Required, (n ≥ 5), should meet Horwitz, see §1.3.1

Appendix 2 Summary of the most important requirements for pre- and post-registration methods for residue-analytical methods (NL framework)

Required	Pre-registration	Post-registration
Description of the method	Complete description required	Complete description required
Analytical method based on generally available laboratory equipment and laboratory facilities	Not required	Required
Avoidance dangerous chemicals	Not required	Required, the use of Diazomethane (or its salts) for derivatisation is not permitted, unless it is demonstrated that there is no other possibility; the use of an LCMS should also be considered.
Derivatisation	Permitted, but the necessity must be explained when used; supplementary validation	Permitted, but the necessity must be explained when used; supplementary validation
MultiResiduMethod	Not required	Required, unless it can be demonstrated that the analyte cannot be included in an (existing) multi-residue method. A specific method is required in that case.
Validation in each matrix	Required, but for the residue-analytical methods for plant products limited validation is sufficient within the same crop group (additional validation: average recovery / accuracy based on n ≥ 2 concentration levels and repeatability / precision based on n ≥ 3 replicates per level)	Required, but for the residue-analytical methods for plant products one sample matrix per crop group is sufficient, see RIVM [9]
Validation report for compounds	all components of the residue definition	all components of the residue definition
Confirmatory method	Recommended where method is not specific	Required, unless the first method is sufficiently specific to determine identity
Independent laboratory validation (ILV)	Not required	Required, but for the residue-analytical methods for plant products validation of 2 crop groups is sufficient; for the residue-analytical methods for animal products validation of 2 animal products is sufficient

Limit Of Quantification (LOQ)	Required Plant/animal: LOQ at 'relevant level' Soil: LOQ ≤ 0.05 mg/kg or ≤ NOEL or LC_{50} Drinking water: LOQ ≤ 0.1 µg/l Surface water: LOQ ≤ $NOEC_{daphnia}$ or $EC_{50\ algae}$ µg/l Air: not applicable	Required Plant/animal: LOQ <= 0.1 mg/kg or LOQ = 0.5-1x MRL where MRL is lower than 0.1 mg/kg. Soil: LOQ ≤ 0.05 mg/kg Drinking water: LOQ ≤ 0.1 µg/l Surface water: LOQ ≤ 0.1 µg/l and < $NOEC_{daphnia}$ of $EC_{50\ algae}$ µg/l Air: see SANCO/825/00 for calculation LOQ
Range of the method	Plant/animal: LOQ-10xLOQ or LOQ-expected residue levels/MRL (whichever is widest) Other: LOQ-10xLOQ	Plant/animal: LOQ-10xLOQ or LOQ/MRL (whichever is widest) Other: LOQ-10xLOQ
Calibration model (linearity or other)	Required Preferably expressed in mg/kg matrix Based on 5 concentration levels or based on 3 duplicate concentration levels Correlation coefficient ≥ 0.99	Required Preferably expressed in mg/kg matrix Based on 5 concentration levels or based on 3 duplicate concentration levels Correlation coefficient ≥ 0.99
Interference of matrix	Required, < 0.3*LOQ (n ≥ 2)	Required, < 0.3*LOQ (n ≥ 2)
Specificity and identity	Required (identification) Interference of metabolites, isomers etc. if necessary for risk assessment	Required (identification)
Accuracy / average recovery	Required n ≥ 5 at 2 concentration levels (LOQ and 10*LOQ) 70-110% Plant/animal: read *expected residue levels/MRL* instead of *10xLOQ* (whichever is highest)	Required n ≥ 5 at 2 concentration levels (LOQ and 10*LOQ) 70-110% Plant/animal: read *MRL* (if any) instead of *10xLOQ* (whichever is highest)
Repeatability (relative standard deviation)	Required n ≥ 5 at 2 concentration levels (LOQ and 10*LOQ) Plant/animal: read *expected residue levels/MRL* instead of *10xLOQ* (whichever is highest) RSD < 20%	Required n ≥ 5 at 2 concentration levels (LOQ and 10*LOQ) Plant/animal: read *expected MRL* instead of *10xLOQ* (whichever is highest) RSD < 20%
Internal standard	No specific requirements	Where used to calculate concentration, it should be demonstrated that the recovery and repeatability of the internal standard are comparable to the analytes
Extraction efficiency	No specific requirements	The extraction procedures used in residue analytical methods for the determination of residues in plants, plant

		products, foodstuff (of plant and animal origin) and in feeding stuff should be verified for all matrix groups for which residues ≥ LOQ are expected.

Appendix 3 Definition terms

	Linearity (Lineariteit)	Precision (Precisie)	Trueness (Juistheid)	Selectivity (Selectiviteit)	Limit of Quantification /Quantification (Bepalingsgrens)
Definition	Linear relationship between response and amount (concentration) of the component to be determined	The closeness of agreement in the analytical results of the same sample	Extent of the agreement between the average of a series of measured values and the actual value	The property of a method to distinguish between the component to be determined and other substances (such as exclusion of Interference/interferin g effects)	Lowest concentration of the component in the sample of which the measured value can still be determined with a certain (un)certainty
Other frequently used terms		ruggedness	Accuracy is often used, although not fully correct	The term specificity is often used. An analytical method is specific where it only reacts to the component to be determined. Specificity can be considered as the ultimate selectivity	Limit of determination (not to be confused with limit of detection)
How determined		Repeatability RSD Reproducibility	Trueness can be determined by means of recovery after addition of a standard (standard addition)		

4. 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 Bgb: Plant protection products and Biocides Decree. See www.overheid.nl/wetten
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 Directive 98/83/EEC (remark: Directive 80/778/EEC was declared invalid by the European Court on 18 June 1996, and has been replaced by 98/83/EEC)
8 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
9 Classification of crops grown in or imported into the European Union for pesticide residue assessment. Report 613340006/2003. RIVM, the Netherlands, 2003.