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

EU part

Plant Protection Products

Chapter 4 Human toxicology; risk operator, worker bystander and resident

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Chapter 4 Human toxicology; risk operator, worker, bystander and resident

Category: Plant protection products

GENERAL INTRODUCTION

This chapter describes the methodology for estimation of the risk of the application of plant protection products to operator, worker, bystander and resident for the EU framework (§1 - §1.5) under 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

The purpose of the risk assessment for operator, worker, bystander or resident is to establish whether the application of a plant protection product has no adverse consequences for these groups of people. For this purpose the endpoints as described in Chapter 4 Human toxicology; mammalian toxicity dossier are compared with the expected exposure.

1.2. Data requirements

The data requirements regarding operator, worker, bystander and resident exposure are described in the Chapter Human toxicology; mammalian toxicity dossier, §1.2.2.

1.3. Risk assessment

To assess whether the application of a plant protection product has no adverse consequences for operator, worker, bystander and resident, the endpoints from the toxicological dossier and the corresponding reference value (e.g. AOEL) (see Chapter 4 Human toxicology; mammalian toxicity dossier) must be compared with the expected exposure.
This chapter describes the EU-methodology for the exposure estimation.

1.3.1 Estimation of operator exposure

The exposure of the person who applies plant protection products (operator) is preferably assessed on the basis of exposure studies, carried out in accordance with the current guidelines [4]. Where such studies are missing, first an exposure estimation is prepared with generic or more specific models.
Supplementary data on actual exposure can be requested if necessary, based on this risk assessment.

Two models are generally used in the EU for estimation of the exposure to plant protection products. These are the German (DE) and the English (UK) model. These models were primarily developed for the application conditions in the separate countries.

For the approval of an active substance, a working arrangement has been made that, until a European harmonised model is available, a safe application estimated with the DE or UK model is sufficient for inclusion in Commission Implementing Regulation (EU) No 540/2011 [3] except for exposure estimation for applications in greenhouses. This working arrangement leaves Member States to choose a different, well justified procedure in the national evaluations.
The NL greenhouse model is specifically developed for estimation of exposure for various activities in greenhouses. In the EU framework, modules available in the DE model (manual upward spraying) or the UK model (manual downward spraying) which are not specific for applications in greenhouses are sometimes also used for applications in greenhouses. Recently a new greenhouse model has been developed, especially for greenhouses in the Mediterranean countries (ECPA greenhouse model).

Exposure is first estimated for the unprotected operator in normal working clothes. Where necessary, the effect of protective measures is taken into account in a later phase of the evaluation.

The models contain default values for the effectiveness of protective measures. In the German model the effectiveness of the protective measures ranges from a factor 1.25 to a factor 100, depending on the type of protective measure. The maximum factor for effectiveness of protective measures in the UK model is 20.

Suitable models are not available for a number of applications. While awaiting further research, a qualitative exposure estimation based on expert judgement is made for these applications. Where induced by this risk assessment, supplementary data on actual exposure are requested.

Calculation of the systemic exposure
External exposure is adjusted for route-specific absorption to calculate systemic exposure.

Uptake after dermal exposure
Insight in the extent to which the skin absorbs a substance and/or formulation after exposure to a relevant level is important for calculation of systemic exposure.
A description of the method used to determine dermal absorption is given in the Chapter Human toxicology; mammalian toxicity dossier, §1.3.5 (EU part of the Evaluation Manual).

Uptake after respiratory exposure
The level of systemic exposure requires insight in the extent to which a substance and/or formulation is taken up in the body via inhalation after exposure to a relevant level.
A default value of 100% is applied where no suitable data on respiratory absorption at the respiratory NOAEL are available.

1.3.2 Estimation of worker exposure (re-entry)

The exposure of workers is preferably assessed on the basis of exposure studies, carried out in accordance with the current guidelines [4]. Where such studies are not available, first an exposure estimation is prepared with generic or more specific models. Supplementary data on actual exposure can be requested if necessary, based on this risk assessment.

No implemented model is available for estimation of worker exposure. For the time being, different models are used in the EU in DARs and core dRRs:

- the module for re-entry from EUROPOEM II.
  The module for re-entry is the so-called Dislodgeable Foliar Residue (DFR) model. This DFR model is described in TNO report V3642 [5]. In 2004 new transfer coefficients have been laid down for EUROPOEM II:
  vegetables: 0.25 m^2/hour
  fruit (from trees): 0.45 m^2/hour
  strawberries: 0.3 m^2/hour
  ornamental crops: 0.5 m^2/hour (not changed in comparison with TNO report)

  The formula for dermal exposure calculation in the DFR model is:
  dermal exposure = DFR x TC x D(f) X T

  DFR = dislodgeable foliar residue at time of re-entry
  TC = transfer coefficient
  T = duration of the activity considered
  D(f) = dissipation function

  A default DFR of 30 mg/m^2 can be used for a conservative evaluation; this applies for a standardised application of 1 kg a.s./ha.
  The DFR model is used for a large number of applications, including applications in greenhouses.
- The NL greenhouse model is also accepted for a number of applications in greenhouses. This model is based on a number of studies carried out in the Netherlands. The results of these studies have been used for the development of a specific model for exposure estimation during re-entry work in ornamental crops (cutting and sorting/bundling); default values are 3 hours cutting and 3 hours sorting/bundling per day (i.e., 6 hours effective crop contact per day).
- The German re-entry model (Krebs et al. 2000, Uniform principles for ensuring health protection for workers when re-entering treated crops following the application of plant

protection products) is also used. The paper has been converted into a computer-supported mathematical model which is freely available online.

1.3.3 Estimation of bystander and resident exposure

No implemented model is available for estimation of the exposure of bystanders or residents.

This is a gap in the evaluation methodology. For the time being, this aspect is in the EU approached in different ways:

- Available field studies, carried out in accordance with the current guidelines, are directly used.
- EUROPOEM II module for bystander exposure, based on field studies, can be used.
- The German model for bystander and resident exposure (Martin et al. 2008 [6]), based on field studies, can be used.
- The UK model for bystander and resident exposure [7], based on field studies, can be used.
- For applications in greenhouses it is assumed that work is carried out under good agricultural practice; this means that during application no bystanders are present in the greenhouse. For exposure of residents near greenhouses, e.g. during ventilation, no EU implemented models are available.

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 human toxicology and operator risk are presented below.

3. Criteria for the approval of an active substance

3.1. Dossier
The dossiers submitted pursuant to Article 7(1) shall contain the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).

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.

3.6. Impact on human health

3.6.1. Where relevant, an ADI, AOEL and ARfD shall be established. When establishing such values an appropriate safety margin of at least 100 shall be ensured taking into account the type and severity of effects and the vulnerability of specific groups of the population. When the critical effect is judged of particular significance, such as developmental neurotoxic or immunotoxic effects, an increased margin of safety shall be considered, and applied if necessary.

3.6.2. An active substance, safener or synergist shall only be approved if, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation EC) No 1272/2008, as mutagen category 1A or 1B.

3.6.3. An active substance, safener or synergist shall only be approved, if, on the basis of assessment of carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.

3.6.4. An active substance, safener or synergist shall only be approved if, on the basis of assessment of reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005.

3.6.5. An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not considered to have endocrine disrupting properties that may cause adverse effect in humans, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005.

By 14 December 2013, the Commission shall present to the Standing Committee on the Food Chain and Animal Health a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties to be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 79(4).

Pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties.

In addition, substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties.

Point 4 of Annex II of Regulation (EC) No 1107/2009 gives criteria for substitution. The texts specifically applicable to the aspect human toxicology and operator risk are presented below. In the chapter “Generic aspects” of this Evaluation Manual, more information is provided on criteria for substitution.

4. Candidate for substitution

An active substance shall be approved as a candidate for substitution pursuant to Article 24 where any of the following conditions are met:

- its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories,
- there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones),
- it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3,
- it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4,
- if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5.

Point 5 of Annex II of Regulation (EC) No 1107/2009 gives information on low risk substances. The texts specifically applicable to the aspect human toxicology and operator risk are presented below. In the chapter “Generic aspects” of this Evaluation Manual, more information is provided on low risk substances.

5. Low-risk active substances
An active substance shall not be considered of low risk where it is or has to be classified in accordance with Regulation (EC) No 1272/2008 as at least one of the following:
- carcinogenic,
- mutagenic,
- toxic to reproduction,
- sensitising chemicals,
- very toxic or toxic.

It shall also not be considered as of low risk if:
- it is deemed to be an endocrine disrupter, or
- it has neurotoxic or immunotoxic effects.

1.4.2 Evaluation of plant protection products

The principles for the evaluation (the Uniform Principles) regarding mammalian toxicology are presented in Commission Regulation (EU) No 546/2011 [8]. These concern the relevant sections of the introductory principles, the general principles and the specific principles Effect on the health of humans and animals.
The specific principles Effect on the health of humans and animals are in the text below printed in a grey frame. This text, including numbering, is the literal text from Commission Regulation (EU) No 546/2011.

2.4. Impact on human or animal health

2.4.1. Impact on human or animal health arising from the plant protection product

2.4.1.1. Member States shall evaluate operator exposure to the active substance and/or to toxicologically relevant compounds in the plant protection product likely to occur under the proposed conditions of use (including in particular dose, application method and climatic conditions) using by preference realistic data on exposure and, if such data are not available, a suitable, validated calculation model.
(a) This evaluation will take into consideration the following information:
(i) the toxicological and metabolism studies as provided for in the Annex to Regulation (EU) No 544/2011 and the results of the evaluation thereof including the acceptable operator exposure level (AOEL). The acceptable operator exposure level is the maximum amount of active substance to which the operator may be exposed without any adverse health effects. The AOEL is expressed as milligrams of the chemical per kilogram body weight of the operator. The AOEL is based on the highest level at which no adverse effect is observed in tests in the most sensitive relevant animal species or, if appropriate data are available, in humans;
(ii) other relevant information on the active substances such as physical and chemical properties;
(iii) the toxicological studies provided for in the Annex to Regulation (EU) No 545/2011, including where appropriate dermal absorption studies;
(iv) other relevant information as provided for in the Annex to Regulation (EU) No 545/2011 such as:
- composition of the preparation,
- nature of the preparation,

- size, design and type of packaging,
- field of use and nature of crop or target,
- method of application including handling, loading and mixing of product,
- exposure reduction measures recommended,
- protective clothing recommendations,
- maximum application rate,
- minimum spray application volume stated on the label,
- number and timing of applications;

(b) This evaluation shall be made for each type of application method and application equipment proposed for use of the plant protection product as well as for the different types and sizes of containers to be used, taking account of mixing, loading operations, application of the plant protection product and cleaning and routine maintenance of application equipment.

2.4.1.2. Member States shall examine information relating to the nature and characteristics of the packaging proposed with particular reference to the following aspects:
- the type of packaging,
- its dimensions and capacity,
- the size of the opening,
- the type of closure,
- its strength, leakproofness and resistance to normal transport and handling,
- its resistance to and compatibility with the contents.

2.4.1.3. Member States shall examine the nature and characteristics of the protective clothing and equipment proposed with particular reference to the following aspects:
- obtainability and suitability,
- ease of wearing taking into account physical stress and climatic conditions.

2.4.1.4. Member States shall evaluate the possibility of exposure of other humans (bystanders or workers exposed after the application of the plant protection product) or animals to the active substance and/or to other toxicologically relevant compounds in the plant protection product under the proposed conditions of use.

This evaluation will take into consideration the following information:

(i) the toxicological and metabolism studies on the active substance as provided for in the Annex to Regulation (EU) No 544/2011 and the results of the evaluation thereof, including the acceptable operator exposure level;

(ii) the toxicological studies provided for in the Annex to Regulation (EU) No 545/2011, including where appropriate dermal absorption studies;

(iii) other relevant information on the plant protection product as provided for in the Annex to Regulation (EU) No 545/2011 such as:
- re-entry periods, necessary waiting periods or other precautions to protect humans and animals,
- method of application, in particular spraying,
- maximum application rate,
- maximum spray application volume,
- composition of the preparation,
- excess remaining on plants and plant products after treatment,
- further activities whereby workers are exposed.

In the context of the risk assessment for local effects, a risk assessment (where appropriate qualitatively) should be prepared on the basis of all available data (such as route-specific studies in which local dermal and respiratory effects may occur, including sensitisation – and irritation studies, toxicological studies with repeated exposure, and field data).

1.4.3 Decision making for plant protection products

The principles for the evaluation for decision making are presented in Commission Regulation (EU) No 546/2011 [8].
These concern the relevant sections of the introductory principles, the general principles and the specific principles Effect on human and animal health.
The specific principles Effect on human and animal health are in the text below printed in a grey frame. This text, including numbering, is the literal text from Commission Regulation (EU) No 546/2011.

2.4. Impact on human or animal health

2.4.1. Impact on human or animal health arising from the plant protection product

2.4.1.1. No authorisation shall be granted if the extent of operator exposure in handling and using the plant protection product under the proposed conditions of use, including dose and application method, exceeds the AOEL.

Moreover, the conditions of the authorisation shall be in compliance with the limit value established for the active substance and/or toxicologically relevant compound(s) of the product in accordance with Council Directive 98/24/EC ([*]) and in accordance with Directive 2004/37/EC of the European Parliament and of the Council ([†])

2.4.1.2. Where the proposed conditions of use require use of items of protective clothing and equipment, no authorization shall be granted unless those items are effective and in accordance with the relevant EU provisions and are readily obtainable by the user and unless it is feasible to use them under the circumstances of use of the plant protection product, taking into account climatic conditions in particular.

2.4.1.3. Plant protection products which because of particular properties or if mishandled or misused could lead to a high degree of risk must be subject to particular restrictions such as restrictions on the size of packaging, formulation type, distribution, use or manner of use.

Moreover, those plant protection products may not be authorised for use by non-professional users which are classified as:

(i) acute toxicity category 1 and 2 for any route of uptake, provided the ATE (acute toxicity estimate) of the product does not exceed 25 mg/kg bw for the oral route of uptake or 0,25 mg/l/4h for the inhalation of dust, mist or fume;
(ii) STOT (single exposure), category 1 (oral), provided their classification is due to the presence of classified substances showing significant non-lethal toxic effects at guidance values below 25 mg/kg bw;

[*] OJ L 131, 5.5.1998, p. 11.
[†] OJ L 158, 30.4.2004, p. 50.

(iii) STOT (single exposure), category 1 (dermal), provided their classification is due to the presence of classified substances showing significant non-lethal toxic effects at guidance values below 50 mg/kg bw;
(iv) STOT (single exposure), category 1 (inhalation of gas/vapour), provided their classification is due to the presence of classified substances showing significant non-lethal toxic effects at guidance values below 0,5 mg/l/4h;
(v) STOT (single exposure), category 1 (inhalation of dust/mist/fume), provided their classification is due to the presence of classified substances showing significant non-lethal toxic effects at guidance values below 0,25 mg/l/4h.

2.4.1.4. Waiting and re-entry safety periods or other precautions must be such that the exposure of bystanders or workers exposed after the application of the plant protection product does not exceed the AOEL levels established for the active substance or toxicologically relevant compound(s) in the plant protection product nor any limit values established for those compounds in accordance with the EU provisions referred to in point 2.4.1.1.

2.4.1.5. Waiting and re-entry safety periods or other precautions must be established in such a way that no adverse impact on animals occurs.

2.4.1.6. Waiting and re-entry periods or other precautions to ensure that the AOEL levels and limit values are respected must be realistic; if necessary special precautionary measures must be prescribed.

See for Council Directive 98/24/EC [9] the following website: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:131:0011:0023:EN:PDF.

In the context of the risk assessment for local effects, a risk assessment (where appropriate qualitatively) should be prepared on the basis of all available data (such as route-specific studies in which local dermal and respiratory effects may occur, including sensitisation – and irritation studies, toxicological studies with repeated exposure and field data).

1.5. Developments

- A European harmonised approach for exposure estimation for operator, worker, bystander and resident is expected to be adopted in 2014.

2. 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
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