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

NL part

Plant protection products

Chapter 4 Human toxicology; mammalian toxicity dossier

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ctgb

Board
for the authorisation
of Plant protection products and Biocides

Chapter 4 Human toxicology; mammalian toxicity dossier

Category: Plant protection products

GENERAL INTRODUCTION

This chapter describes the requirements for the authorisation evaluation of a plant protection product and active substances within 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 evaluation for plant protection products. The plant protection product may be authorised if the criteria laid down in Regulation (EC) No 1107/2009 [1] are met, also taken 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].

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.

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

2.1. Introduction

For the aspect Human toxicology, mammalian toxicity dossier, the data requirements for the active substance and product do not differ from 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 accordance with the provisions in EU framework, see EU part of the Evaluation Manual (§1.2).

The studies must be performed in compliance with the applicable guidelines. An overview of the data requirements and guidelines, and whether or not these are required for particular fields of use is given in Appendix A to Chapter 4.

Reduction of laboratory animal use and suffering currently receives much attention.
The Board prefers newly developed studies that are in line with such a regime, such as *in vitro* dermal absorption tests and *in vitro* eye irritation test. As long as these have, however, not yet been included in the applicable OECD and/or EU Directives, a toxicologically justified statement is required if such tests are submitted.

2.2.1. Data requirements for the active substance

No difference with data requirements in EU framework. See EU framework in the EU part of the Evaluation Manual (§1.2).

Supplementary studies on the active substance
(283/2013: 5.8.2)

Supplementary studies on choline-esterase inhibition
Where active substances belong to the group of organophosphates or carbamates, or where the active substance shows acetylcholine-esterase inhibition, acetylcholine-esterase activity should be monitored regularly, in particular in erythrocytes and brain.
The effect of acetylcholine-esterase inhibition should be assessed in acute studies.
The (critical) effect should then, besides all clinical symptoms also be assessed in the semi-chronic, chronic, reproduction and teratogenicity studies.
Background information on acetylcholine-esterase inhibition is given in the RIVM report with fact sheets about acetylcholine-esterase inhibition [7] and the JMPR report [8].

Supplementary studies on eye defects (cataract)
Studies on cataractogenic properties is mandatory for nitro compounds.
This study is described in several guidelines; semi-chronic research in accordance with OECD guideline 408, 409, 411 and 413 and in all chronic studies.

Supplementary studies on blood defects
Formation of Heinz bodies, methemoglobin (MetHB) or sulphhemoglobin in the blood should be determined for oxidising compounds such as nitro compounds and chloranilines.
Methemoglobin formation is considered an acute effect. Clinical symptoms that may indicate methemoglobin formation are blue colouring of the extremities and the nose.
Timing of the methemoglobin measurements is very important (not too late, or only at the end of the study).
These effects are preferably assessed in the semi-chronic, chronic, reproduction, and teratogenicity studies. Background information about methemoglobin formation (MetHB) is given in the RIVM report with fact sheets about methemoglobin [7].

2.2.2. Data requirements for the product

There is no difference with the data requirements in the EU framework. See EU framework in the EU part of the Evaluation Manual (§1.2). For dermal absorption and skin sensitisation studies, further clarification of the text given in the EU framework is presented below.

Dermal absorption
(see also §1.2.2 and §1.3.5 in the EU part of the Evaluation Manual)

Exposure assessment is first carried without PPE. If the exposure exceeds the AOEL than for professional use a second assessment is made with the assumptions that PPE is used by the operator and/or worker. No dermal absorption data need to be submitted if no risk is estimated at a default value for dermal absorption [9]. If the AOEL is exceeded with PPE when a default value has been used for dermal absorption, dermal absorption data can be submitted to further refine the risk assessment .

An OECD guideline has been laid down for *in vitro* and *in vivo* dermal absorption studies. In practice, submission of one of these two studies can be sufficient, depending on the results. *In vitro* studies have been found to be very suitable to study species differences in dermal absorption. This is important because the permeability of rat skin to substances is usually higher than that of human skin.

This further implies that reliance on an *in vivo* study with the rat alone might result in an overestimation of the risk for the operator/worker.

According to the Board unnecessary use of laboratory animals must be avoided.
The Board therefore prefers that an *in vitro* study is performed. The Board only considers performance of an *in vivo* study justified if the AOEL is still expected to be exceeded on the basis of the *in vitro* study.

If data on individual tape strips are available, the first two strips will not be included in the total deliverable dose. This strategy is in line with the EFSA Guidance on dermal absorption [9].

Skin sensitisation
(see also §1.2.2 in the EU part of the Evaluation Manual (§1.2)).

The Ctgb prefers, in accordance with EU requirements, a local lymph node assay (LLNA) according to OECD guideline 429. If a Guinea Pig Maximisation Test is performed, a scientific justification must be submitted to explain why this study is preferred over the LLNA. A guinea pig study (Guinea Pig Maximisation Test or a (modified) Buehler test) with the formulated product, however, is not simply rejected. The results of the guinea pig sensitisation study with the substance and the fact whether the formulation contains co-formulants with components with sensitising properties are always taken into account.

For clarification, a number of situations are described below:
- Where the LLNA or a justified maximisation study with the active substance is negative and the formulation contains no co-formulants with sensitising properties, the Ctgb will accept a well performed (modified) Buehler test.
- Where the LLNA or a justified maximisation study with the active substance is negative but the formulation contains co-formulants with sensitising properties, the Ctgb will use mathematical methods (see 99/45/EC) to decide on labelling. Possible negative results from a (modified) Buehler test with the formulation are not simply accepted. The results of an LLNA or a justified maximisation study with the formulation, if available, overrule a possible calculation.
- Where the LLNA or a justified maximisation study with the active substance is positive, the Ctgb will use the calculation rules to decide on labelling (see

99/45/EC). Possible negative results from a (modified) Buehler test with the formulation are not simply accepted.
The results of an LLNA or a justified maximisation study with the formulation, if available, overrule possible a calculation, and the results of the (modified) Buehler.

- Where a (modified) Buehler test with the formulation is clearly positive, such a study is in principle acceptable and performance of an LLNA or a justified maximisation study is not required.

If, according to the applicant, information with regard to acute oral, dermal and inhalatory toxicity, and skin and eye irritation and sensitisation of the formulation obtained by calculation is sufficient, the applicant should submit a toxicologically-based justification as indicated in Regulation (EC) No. 1272/2088.

2.3. Derivation of endpoints and reference values

The evaluation methodologies of toxicity studies for chemical active substances and plant protection products are in accordance with the provisions described in EU part of the Evaluation Manual (§1.3). Further clarification of the EU procedures and specific rules applying to the national approval framework are given below.

2.3.1. Derivation of the list of endpoints for human toxicology

This section gives a further description of the information given under data requirements (see §1.2 in the EU part of the Evaluation Manual and 2.2).

Where for a certain aspect (e.g., mutagenicity, reproduction toxicity etc.) no qualitative and/or insufficient quantitative research is available, no final conclusion or endpoint can be derived for this aspect. Additional information is necessary in such cases.

Each study is summarised separately in the toxicological summary and, where possible, the 'No Observed Adverse Effect Level' (NOAEL) is derived.
The following factors are, among others, taken into account in the derivation of, e.g., a NOAEL [10]:

- toxicological relevance of the effect (adverse versus non-adverse);
- toxicological relevance of the effect for man;
- dose-response relationship;
- statistical significance of the effect;
- relationship between the effect and other effects that occur at higher dose levels.

International developments, as published by WHO, JMPR and OECD, are also taken into account when determining whether certain effects are relevant.

The dose is expressed in mg/kg bw/day. Where food intake is not reported in a study, standard conversion factors are used to convert from ppm to mg/kg bw/day. For rats and mouse the conversion factors are presented in an EFSA guidance document [11]. For rabbit and dog no conversion factors are mentioned in the EFSA guidance and for these species the dose in ppm is divided by 33 and 40, respectively, in case of young adult laboratory animals [12,13].

Genotoxicity and carcinogenicity

The standard genotoxicity package normally includes three *in vitro* tests and one *in vivo* study.
When a substance is negative in the three *in vitro* tests and in an *in vivo* test, it is generally assumed that the substance is not genotoxic.

Where one or more of the *in vitro* tests show a positive result, the substance is intrinsically genotoxic. A specific *in vivo* genotoxicity test is in that case required (see data requirements) with, generally, rat and mouse as animal species.
Where the *in vivo* test is positive as well, the substance is considered genotoxic. Subsequently the relevance of this finding for man is assessed. This may require supplementary research into the mode of action of the substance.

2.3.2. Derivation of the ADI

For derivation of the ADI, the Netherlands applies the same method as in the EU (see §1.3.2 in the EU part of the Evaluation Manual).

2.3.3. Derivation of the AOEL and AEL

Derivation of the AOEL and AEL (for non-professional use) is in accordance with the provisions described in EU part of the Evaluation Manual (§1.3.3). Further clarification of the EU procedures and specific rules applying to the national approval framework are given below.

Deviations from an established EU-AOEL are possible in case the exposure scenario of the proposed use in the Netherlands is not covered by the EU-AOEL (e.g. a semi-chronic AOEL is derived in the EU while in the Netherlands chronic exposure is possible).
If, in the absence of a useful NOAEL, an AOEL is derived from the lowest observed adverse effect level (LOAEL), an additional factor can be applied. A factor of 10 is used as a default value. Information in the dossier, particularly concerning the slope of the dose-response curve, the distance to the probable NOAEL etc. can lead to the use of another factor. The choice must be motivated in the decision-making stage.

If there are significant limitations in the available toxicity data, supplementary data should be generated, as no factor can compensate for these limitations.

There are a number of supplementary remarks:

In the Netherlands, the AOEL/AEL is usually also expressed in mg/person/working day. An average body weight of 70 kg is assumed as default value for professional operators (including workers) and 63 kg for the non-professional operator and worker.

Certain applications in the Netherlands are also performed by contract workers. A TNO report with the results of a survey among contract workers was published in 2001 [14].

This survey was performed by the sector organisation of contract workers in the Netherlands, Cumela. Cumela conducted a new survey in 2004. The results show that contract workers may operate in the following crops (with a proportion contract labour >10%): maize, cereals, beet, potatoes, onions, grassland, asparagus, vegetables for processing, and other field vegetables, other vegetable crops (e.g., oilseed rape, flax, oil-containing crops), tree nursery stock, public parks and gardens, recreation grasses and uncultivated land.
The expected exposure duration for a contract worker will be evaluated per application, on the basis of which a decision will be taken whether a semi-chronic or chronic AOEL needs to be derived.

2.3.4. Derivation of the ARfD

The NL method for derivation of the ARfD is the same as in the EU (see §1.3.4 in the EU part of the Evaluation Manual).

2.3.5. Derivation of the dermal absorption value for the list of endpoints

The Netherlands follows the EFSA Guidance on dermal absorption [9] (see also §1.3.5 in the EU part of the Evaluation Manual), in accordance with the procedure in the EU, for derivation of the human dermal absorption value for the list of endpoints.

The dermal absorption given in the EU list of endpoints is usually specific for a certain formulation concentrate and spray dilution. In many cases it cannot be used for the calculation of the systemic exposure for NL applications. The extent of dermal absorption is affected by various factors such as co-formulants and exposure level (area dose) and is not an intrinsic property of the substance.

2.3.6. Combination of two or more active substances in a product

Combination toxicity should be determined for a plant protection product that contains several active substances, as well as for combinations of plant protection products of which the combination (tank mix) is recommended in the instructions for use.
The acute toxicity of the product is known (= data requirements product) for plant protection products with several active substances. A risk assessment should, however, also be performed for repeated exposure to the combination of two or more active substances.

This is not part of the EU data requirements. This aspect is, however, given attention in the national evaluations. Combined exposure to substances may possibly lead to a different toxicological profile than the profile derived for the individual substances because they may interact.
Aspects considered in the evaluation include the toxicological profile (critical effect, mode of action), metabolism of the substances, and whether the substances cause enzyme induction.
Two or more substances may have an additive, synergistic or antagonistic effect on each other's activity. A synergistic or antagonistic effect, however, requires that exposure takes place at or near the level at which undesirable effects of the individual substances may be expected (in comparison with the AOEL/ADI/ARfD).

Current Commission Regulation (EU) No 284/2013 [6] requirements in the EU only concern combinations of products.

2.4. Approval

The actual decision whether a plant protection product can be authorised follows from the risk evaluation for operator, worker, bystander, resident and consumers, which is elaborated in Chapter 4 Human toxicology, risk operator, worker and bystander and Chapter 5 Residues, risk for consumers in the NL part of the Evaluation Manual.

2.5. Developments

Developments in the EU framework (see under §1.5 in the EU part of the Evaluation Manual) will also affect the data requirements and evaluation methodologies in the NL framework in view of the aim of the largest possible harmonisation of data requirements and evaluation methods.

3.REFERENCES

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