# Evaluation Manual for the Authorisation of plant protection products and biocides

## NL part

## Biocides

## Chapter 4 Human toxicology; Human Toxicity dossier

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**Author:**
**Dr. Saskia Bosman**

**Lay-out:**
**Jiske de Wolf**

ctgb

**Board**
**for the authorisation**
**of plant protection products and biocides**

# Chapter 4 Human toxicology; toxicological dossier
Category: biocides

# 1. GENERAL INTRODUCTION

This chapter (NL tox part) describes the data requirements for estimation of the human toxicological effects of a biocide and the active substance, and how limit values are derived for the NL framework.

# 2. NL FRAMEWORK

The NL framework describes the authorisation evaluation of biocides based on existing substances, included in Annex I, and new active substances. A new substance is a substance not authorised in any of the EU Member States on 14 May 2000.
The pesticide that contains such substances may be authorised if the testing criteria laid down in the Plant Protection Product and Biocide Act (Wgb) 2007 [1] are met. The product is tested against the Plant Protection Product and Biocide Regulations (RGB) [2]. The evaluation dossiers must meet Annex IIA, IIB, IIIA and IIIB of 98/8/EC

The NL framework describes the data requirements and “criteria and trigger” (derivation endpoints and limit values) values for which specific rules apply in the national testing framework or where the national testing framework has been elaborated in more detail than the EU framework.

The NL procedure described in this chapter is used for evaluation of a substance for inclusion in Annex I in case no EU procedure has been described.

## 2.1. Introduction

In general, for the aspect human toxicology, toxicological dossier, the data requirements for active substance and product do not differ from the EU framework (see paragraph 2.2). The NL procedure is only described if no EU procedure has been described. For the aspect Human toxicology, toxicological dossier, the testing framework with criteria and trigger values in the RGB differ for some points from the EU framework (see paragraph 2.3).

## 2.2. Data requirements

The data requirements for biocides are in accordance with the provisions in EU framework (see EU part). The data requirements for which in the national testing framework specific rules apply, or where the national testing framework has been elaborated in more detail than in EU framework has been described further in this paragraph.

Experiments carried out after 25 July 1993 must have been carried out under GLP.

Reduction of test 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* sensitisation tests. To predict strong and irreversible (corrosive) effects, alternative methods, which avoid animal testing may also be submitted as pre-screening tests (the Bovine Cornea Opacity and Permeability (BCOP) test, Hen’s Egg test Corio-Allantois-Membrane (HET CAM), Chicken Enucleated Eye test (CEET) and Isolated Rabbit Eye (IRE) Test. As long as these have, however, not yet been included in the applicable OECD and/or EU Directives, a toxicologically justified position statement is required if such tests are submitted.

### *2.2.1 Data requirements active substance*

*Dermal absorption*
(see also EU part).
The EU Application Form requests *in vivo* (rat) and *in vitro* (rat/man) dermal absorption studies.

No data need to be submitted if no risk without PPE is estimated at 100% dermal absorption. This also applies if calculations can be based on a lower default value of 10% based on physico-chemical properties. Another assumption that can be done is that dermal absorption will not be higher than oral absorption. If the AEL is exceeded without PPE when a default value has been used for dermal absorption, dermal absorption data should be submitted.

An OECD guideline has been laid down for both types of 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 AEL is still expected to be exceeded on the basis of the *in vitro* study.

If data on individual tape strips are available, in principle the first two strips will not be included in the total deliverable dose (see EU part). This strategy is in line with the EFSA Agreements made in the expert meetings and the updated dermal absorption guidance in 2012 [5].

*Skin sensitisation*
The CTB prefers a local lymph node assay (LLNA test; OECD 429) or Guinea Pig Maximisation Test. Where a (modified) Buehler test is carried out, a scientific justification must be submitted why this study is preferred over the other tests.

### *2.2.2 Data requirements product*

*Dermal absorption*
See §2.2.1 Data requirements active substance, 6.2 Metabolism studies in mammals [Ann IIA, VI. 6.2.]

*Skin sensitisation*
The Ctgb prefers, in accordance with EU requirements, a local lymph node assay (LLNA test) according to OECD guideline 429 or a Guinea Pig Maximisation Test. If a (modified) Buehler test is performed, a scientific justification must be submitted to explain why this study is preferred over the other tests. For studies with the formulated product, however, a (modified) Buehler test is not simply rejected. The results of the sensitisation study with the substance and the fact whether the formulation contains co-formulants with components with sensitising properties are always taken into account.
In case a (modified) Buehler test has been submitted, a scientific justification should always be provided why this test has been performed.
For clarification, a number of situations are described below:

- Where the maximisation study with the 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 maximisation study with the 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 maximisation study with the formulation, if available, overrule a possible calculation.
- Where the maximisation study with the 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 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 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 99/45/EC.

## 2.3. Derivation endpoints and limit values (EU procedures elucidated)

The risk assessment is based on the toxicological endpoints derived from the submitted studies. There is no difference with the evaluation methodologies of toxicity studies as described in EU framework (see EU part). The EU procedures are elucidated below.

Each study is summarised separately in the toxicological summary and, where possible, under derivation of the corresponding 'No Observed Adverse Effect Level' (NOAEL). Dose-response relationships are, e.g., taken into account when deriving an NOAEL. The unit mg/kg bw/day is used for dose. Where food intake has not been reported in a study, standard conversion factors are used to convert from ppm to mg/kg bw/day. For mouse, rabbit, rat and dog the dose in ppm is divided by 10, 33, 20 and 40, respectively, in the case of young adult test animals [3, 4]. A conversion factor of 15 is used to convert from ppm to mg/kg bw/day in a reproduction toxicity study.

The Netherlands follows the EU Guidance document on dermal absorption [5], in accordance with the procedure in the EU, for derivation of the human dermal absorption value for the endpoints list.
The dermal absorption given in the EU endpoints list does not necessarily need to be used for 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.

### *2.3.1 Derivation AEL / MOE derivation*

The MOE approach is not used in the Netherlands, because it is a dated method not easily be used for route-to-route extrapolation.
The Netherlands applies the same method as in the EU (see EU part) for derivation of the AEL.

### *2.3.2 Derivation ADI and ARfD*

For derivation of the ADI and ARfD, the Netherlands applies the same methods as in the EU (see EU part).

### *2.3.3 Derivation dermal absorption*

The Netherlands follows the EU Guidance document on dermal absorption ([5] see also EU part), in accordance with the procedure in the EU, for derivation of the human dermal absorption value.

The dermal absorption derived in support of the EU evaluation does not necessarily need to be used for 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.

## 2.4 Derivation endpoints and limit values (NL specific procedures)

For the testing frame work with criteria and trigger values used in the national authorisation reference is made to the Plant Protection Products and Biocides Regulations (RGB). Article 3.7 (new and existing substances including in Annex I) describes the authorisation criteria. The Rgb indicates that a health based reference value for systemic effects should be derived, based on either the AEL or the limit value from the 'Arbeidsomstandighedenbesluit', the Tolerable Limit Value (TLV), and formerly known as MAC-value.

The texts specifically referring to the endpoints and limit values is given below in the grey frame (in Dutch):

**Artikel 3.7. Gezondheidskundige norm**

**1.** Het college bepaalt voor elke voor de toelating relevante blootstelling de gezondheidskundige norm voor systemische effecten op de gezondheid door blootstelling via de orale, dermale en inhalatoire blootstellingsroute.

**2.** De blootstelling wordt voor iedere blootstellingsroute uitgedrukt in mg/persoon per dag en voor vluchtige stoffen de inhalatoire blootstellingsroute tevens uitgedrukt in mg/$m^3$.

**3.** Het college maakt bij de bepaling van de gezondheidskundige norm gebruik van het Acceptable Operator Exposure Level (AOEL) zoals voortkomend uit de beoordeling van de werkzame stof in de biocide door de Commissie van de Europese Gemeenschappen, bedoeld in de artikelen 10 en 11 van Richtlijn 98/8/EG, en de grenswaarde zoals vastgesteld krachtens art. 4.3, eerste lid, van het Arbeidsomstandighedenbesluit.

**4.** In aanvulling op het tweede lid bepaalt het college in geval van blootstelling aan stoffen met kankerverwekkende effecten zonder toxicologische drempelwaarde het risicogetal. Dit risicogetal wordt overeenkomstig het eerste lid aangemerkt als gezondheidskundige norm.

**5.** Het college bepaalt voor zover mogelijk op grond van het dossier in alle gevallen de gezondheidskundige norm voor lokale effecten op de gezondheid door blootstelling voor de orale, dermale en inhalatoire blootstellingsroute voor kortdurende alsmede langdurige blootstelling. Deze effecten worden:

- bij de dermale effecten uitgedrukt in mg/persoon per dag en
- bij inhalatoire effecten uitgedrukt in mg/$m^3$ in de inademingslucht per persoon per dag.

**6.** Wanneer uit de risicobeoordeling bedoeld in bijlage VI bij richtlijn 98/8/EG blijkt dat de risico-index zonder gebruik van persoonlijke beschermingsmiddelen groter is dan 1, wordt de gezondheidskundige norm met uitzondering van die voor kankerverwekkende effecten zonder toxicologische drempelwaarde, opnieuw berekend met behulp van de methode allometrische

extrapolatie en wordt de risico-index opnieuw bepaald.

**7.** Wanneer na toepassing van het zesde lid de risico-index bij de dermale blootstellingsroute groter is dan 1, wordt bijlage IIB, puntl 6.4, bij richtlijn 98/8/EG toegepast. Het college bepaalt de risico-index bij de dermale blootstellingsroute met behulp van de experimenteel verkregen nieuwe informatie opnieuw.

In this evaluation manual specific evaluation methods resulted from the descriptions in the RGB artikel 3.7 gezondheidskundige norm lid 3 and 4, not identical in detail to the EU evaluation method described in the EU part, are elaborated in this paragraph.

*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.

For substances holding a risk of tumour formation through direct effects on genetic material (genotoxic carcinogenesis) a risk value should be determined. This is indicated in the Rgb. Other mechanisms of tumour formation allow a threshold approach: there is an exposure level at which the effect does not occur.

For substances with intrinsic (*in vitro*) genotoxic properties, but for which these properties are not expressed in *in vivo* genotoxicity tests and in chronic/carcinogenicity studies, the approach is as follows:
Where sufficient (animal) experimental evidence exists for the non expression of genotoxicity *in vivo,* a limit value approach is followed in the risk assessment (the NOAEL from the chronic/carcinogenicity studies, usually based on general toxic effects because tumour formation is usually not the most sensitive effect). However, the margin between the NOAEL for tumour formation and the overall NOAEL of the study should be taken into account. No additional safety factor is required if this margin is large enough (about a factor of 10).

In the Netherlands for non-genotoxic carcinogenic compounds a life-time risk value based on a report of the Health Council of the Netherlands will be used. Ministry of Social Affairs and Employment (SZW) chooses to derive a limit value – the risk value (“risicogetal”) – that indicates the chance of 4 additional deaths due to cancer per 100.000 during a 40 year professional exposure (see definitions in the RGB).
In the EU cancer risk methodologies are proposed by REACH, EFSA and U.S. EPA mentioned in the in Ch 4.1.TNsG on Annex I inclusion, chapter 4.1 (see also the EU part).

*Gezondheidskundige norm / grenswaarde (arbeidsomstandigheden besluit)*
In practice, the AEL will generally be the most critical value (see EU tox part)
This means that this may also be a different value obtained on the basis of the Dutch Occupational Health and Safety Act (ARBO) such as the Tolerable limit values, formerly known as MAC-values (as indicated in the Uniform Principles, 2.4.1.1.).

**2.5 Approval**
The actual decision whether a biocide can be authorised follows from the risk assessment for primary and secondary exposure. Both are discussed in EU and NL exposure part.

**2.6 Developments**
Developments in EU framework will also affect the data requirements and testing framework with criteria and trigger values (derivation endpoints and limit values) in NL framework because the largest possible harmonisation of data requirements and testing framework for criteria and trigger values is aimed for.

## 3. REFERENCES

1. Wgb: Plant Protection Products and Biocides Act 2007.
2. Rgb : The Plant Protection Products and Biocides Regulations.
3. Paulussen, J.J.C., Mahieu, C.M., Bos, P.M.J. Default values in occupational risk assessment, TNO report V98.390 (1998).
4. Assessment factors for human risk assessment, RIVM Factsheet FSV-004/00 (2001).
5. Guidance Document on Dermal Absorption. Sanco/222/2000 rev. 7, d.d. 19 March 2004. http://europa.eu.int/comm/food/plant/protection/evaluation/guidance/wrkdoc20_rev_en.pdf. and the updated EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665)