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B.W.J.G. Mensink

Environmental risk limits for difenoconazole

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B.J.W.G. Mensink

Contact:
C.E. Smit
Expertise Centre for Substances
ce.smit@rivm.nl

This investigation has been performed by order and for the account of Directorate-General for Environmental Protection, Directorate for Soil, Water and Rural Area (BWL), within the framework of the project 'Standard setting for other relevant substances within the WFD'.

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Rapport in het kort

Environmental risk limits for difenoconazole

Dit rapport geeft milieurisicogrenzen voor het fungicide difenoconazool in water. Milieurisicogrenzen zijn de technisch-wetenschappelijke advieswaarden voor de uiteindelijke milieukwaliteitsnormen in Nederland. De milieurisicogrenzen zijn afgeleid volgens de methodiek die is voorgeschreven in de Europese Kaderrichtlijn Water. Hierbij is gebruikgemaakt van de beoordeling in het kader van de Europese toelating van gewasbeschermingsmiddelen (Richtlijn 91/414/EEG), aangevuld met gegevens uit de openbare literatuur.

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1 Introduction

1.1 Background and scope of the report

In this report, environmental risk limits (ERLs) for surface water are derived for the fungicide difenoconazole. The derivation is performed within the framework of the project 'Standard setting for other relevant substances within the WFD', which is closely related to the project 'International and national environmental quality standards for substances in the Netherlands' (INS). Difenoconazole is part of a series of 25 pesticides that appeared to have a high environmental impact on the evaluation of the policy document on sustainable crop protection ('Tussenevaluatie van de nota Duurzame Gewasbescherming'; MNP, 2006) and/or were selected by the Water Boards ('Unie van Waterschappen'; project 'Schone Bronnen'; <http://www.schonebronnen.nl/>).

The following ERLs are considered:

- Maximum Permissible Concentration (MPC) – the concentration protecting aquatic ecosystems and humans from effects due to long-term exposure
- Maximum Acceptable Concentration (MAC_{eco}) – the concentration protecting aquatic ecosystems from effects due to short-term exposure or concentration peaks.
- Serious Risk Concentration (SRC_{eco}) – the concentration at which possibly serious ecotoxicological effects are to be expected.

More specific, the following ERLs can be derived depending on the availability of data and characteristics of the compound:

| | |
|-------------------------------|---|
| MPC _{eco, water} | MPC for freshwater based on ecotoxicological data (direct exposure) |
| MPC _{sp, water} | MPC for freshwater based on secondary poisoning |
| MPC _{hh food, water} | MPC for fresh and marine water based on human consumption of fishery products |
| MPC _{dw, water} | MPC for surface waters intended for the abstraction of drinking water |
| MAC _{eco, water} | MAC for freshwater based on ecotoxicological data (direct exposure) |
| SRC _{eco, water} | SRC for freshwater based on ecotoxicological data (direct exposure) |
| MPC _{eco, marine} | MPC for marine water based on ecotoxicological data (direct exposure) |
| MPC _{sp, marine} | MPC for marine water based on secondary poisoning |
| MAC _{eco, marine} | MAC for marine water based on ecotoxicological data (direct exposure) |

1.2 Status of the results

The results presented in this report have been discussed by the members of the scientific advisory group for the INS-project (WK-INS). It should be noted that the Environmental Risk Limits (ERLs) in this report are scientifically derived values, based on (eco)toxicological, fate and physico-chemical data. They serve as advisory values for the Dutch Steering Committee for Substances, which is appointed to set the Environmental Quality Standards (EQSs). ERLs should thus be considered as proposed values that do not have any official status.

2 Methods

The methodology for the derivation of ERLs is described in detail by Van Vlaardingen and Verbruggen (2007), further referred to as the ‘INS-Guidance’. This guidance is in accordance with the guidance of the Fraunhofer Institute (FHI; Lepper, 2005).

The process of ERL-derivation contains the following steps: data collection, data evaluation and selection, and derivation of the ERLs on the basis of the selected data.

2.1 Data collection

In accordance with the WFD, data of existing evaluations were used as a starting point. For pesticides, the evaluation report prepared within the framework of EU Directive 91/414/EC (Draft Assessment Report, DAR) was consulted (EC, 2006; further referred to as DAR). An on-line literature search was performed on TOXLINE (literature from 1985 to 2001) and Current Contents (literature from 1997 to 2007). In addition to this, all potentially relevant references in the RIVM e-tox base and EPA’s ECOTOX database were checked.

2.2 Data evaluation and selection

For substance identification, physico-chemical properties and environmental behaviour, information from the List of Endpoints of the DAR was used. When needed, additional information was included according to the methods as described in Section 2.1 of the INS-Guidance. Information on human toxicological threshold limits and classification was also primarily taken from the DAR.

Ecotoxicity studies (including bird and mammal studies) were screened for relevant endpoints (i.e. those endpoints that have consequences at the population level of the test species). All ecotoxicity and bioaccumulation tests were then thoroughly evaluated with respect to the validity (scientific reliability) of the study. A detailed description of the evaluation procedure is given in the INS-Guidance (see Section 2.2.2 and 2.3.2). In short, the following reliability indices were assigned:

- Ri 1: Reliable without restriction
'Studies or data ... generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline ... or in which all parameters described are closely related/comparable to a guideline method.'
- Ri 2: Reliable with restrictions
'Studies or data ... (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.'
- Ri 3: Not reliable
'Studies or data ... in which there are interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated

according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgment.'

- Ri 4: Not assignable

'Studies or data ... which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).'

All available studies were summarised in data-tables, that are included as Appendices to this report. These tables contain information on species characteristics, test conditions and endpoints. Explanatory notes are included with respect to the assignment of the reliability indices.

With respect to the DAR, it was chosen not to re-evaluate the underlying studies. In principle, the endpoints that were accepted in the DAR were also accepted for ERL-derivation with Ri 2, except in cases where the reported information was too poor to decide on the reliability or when there was reasonable doubt on the validity of the tests. This applies especially to DARs prepared in the early 1990s, which do not always meet the current standards of evaluation and reporting.

In some cases, the characteristics of a compound (i.e. fast hydrolysis, strong sorption, low water solubility) put special demands on the way toxicity tests are performed. This implies that in some cases endpoints were not considered reliable, although the test was performed and documented according to accepted guidelines. If specific choices were made for assigning reliability indices, these are outlined in Section 3.3 of this report.

Endpoints with Ri 1 or 2 are accepted as valid, but this does not automatically mean that the endpoint is selected for the derivation of ERLs. The validity scores are assigned on the basis of scientific reliability, but valid endpoints may not be relevant for the purpose of ERL-derivation (e.g. due to inappropriate exposure times or test conditions that are not relevant for the Dutch situation).

After data collection and validation, toxicity data were combined into an aggregated data table with one effect value per species according to Section 2.2.6 of the INS-Guidance. When for a species several effect data were available, the geometric mean of multiple values for the same endpoint was calculated where possible. Subsequently, when several endpoints were available for one species, the lowest of these endpoints (per species) is reported in the aggregated data table.

2.3 Derivation of ERLs

For a detailed description of the procedure for derivation of the ERLs, reference is made to the INS-Guidance. With respect to the selection of the final MPC_{water} an additional comment should be made:

2.3.1 Drinking water

The INS-Guidance includes the MPC for surface waters intended for the abstraction of drinking water ($MPC_{dw, water}$) as one of the MPCs from which the lowest value should be selected as the general MPC_{water} (see INS-Guidance, Section 3.1.6 and 3.1.7). According to the proposal for the daughter directive Priority Substances, however, the derivation of the AA-EQS (= MPC) should be based on direct exposure, secondary poisoning, and human exposure due to the consumption of fish. Drinking water was not included in the proposal and is thus not guiding for the general MPC value. The exact way of implementation of the $MPC_{dw, water}$ in the Netherlands is at present under discussion within the framework of the "AMvB Kwaliteitseisen en Monitoring Water". No policy decision has been taken yet, and the $MPC_{dw, water}$ is therefore presented as a separate value in this report. The MPC_{water} is thus derived considering the individual MPCs based on direct exposure ($MPC_{eco, water}$), secondary poisoning

($MPC_{sp, water}$) or human consumption of fishery products ($MPC_{hh food, water}$); the need for derivation of the latter two is dependent on the characteristics of the compound.

Related to this is the inclusion of water treatment for the derivation of the $MPC_{dw, water}$. According to the INN-Guidance (see Section 3.1.7), a substance specific removal efficiency related to simple water treatment should be derived in case the $MPC_{dw, water}$ is lower than the other MPCs. For pesticides, there is no agreement as yet on how the removal fraction should be calculated, and water treatment is therefore not taken into account. In case no A1 value is set in Directive 75/440/EEC, the $MPC_{dw, water}$ is set to the general Drinking Water Standard of 0.1 $\mu\text{g/L}$ for organic pesticides as specified in Directive 98/83/EC.

3 Derivation of environmental risk limits for difenoconazole

3.1 Substance identification, physico-chemical properties, fate and human toxicology

3.1.1 Identity

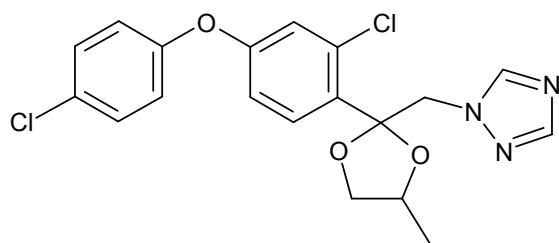


Figure 1. Structural formula of difenoconazole.

Table 1. Identification of difenoconazole.

| Parameter | Name or number | Source |
|----------------------------------|---|-------------|
| Common/trivial/other name | difenoconazole | EC, 2006 |
| Chemical name | 1-[2-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-4-methyl[1,3]dioxolan-2-ylmethyl]-1H-[1,2,4] triazole | EC, 2006 |
| CAS number | 119446-68-3 | EC, 2006 |
| EC number | not allocated | |
| SMILES code | Clc4ccc(Oc1ccc(c(Cl)c1)C2(OCC(O2)C)Cn3ncnc3) | US EPA 2007 |
| Use class | fungicide | EC, 2006 |
| Mode of action | interference with the ergosterol biosynthesis by inhibition of the C-14-demethylation of sterols, which leads to morphological and functional changes of the fungal cell membrane | EC, 2006 |
| Authorised in NL Annex 1 listing | yes | |
| | no | |

3.1.2 Physico-chemical properties

Table 2. Physico-chemical properties of difenoconazole.

| Parameter | Unit | Value | Remark | Reference |
|----------------------|--------------------------|-----------------------|---|------------------|
| Molecular weight | [g/mol] | 406.27 | | |
| Water solubility | [mg/L] | 15 | at a pH of 7.2 | EC, 2006 |
| pK_a | [-] | 1.07±0.18 | the pK_a for deprotonation of the triazole moiety of difenoconazole | EC, 2006 |
| $\log K_{ow}$ | [-] | 4.36 | at pH 8. In agreement with QSARs | EC, 2006, |
| | [-] | 4.57 | ClogP | BioByte, 2006 |
| | [-] | 4.30 | MlogP | BioByte, 2006 |
| KOWWIN | [-] | 5.20 | | |
| $\log K_{OC}$ | [-] | 3.58 | from soil batch experiments; value finally used for leaching calculations | EC, 2006 |
| Vapour pressure | [Pa] | 3.32×10^{-8} | at 25 °C | EC, 2006 |
| Melting point | [°C] | 82-83 | | EC, 2006 |
| Boiling point | [°C] | - | not relevant, decomposes | EC, 2006 |
| Henry's law constant | [Pa.m ³ /mol] | 9.0×10^{-7} | at 20 °C | EC, 2006 |

3.1.3 Behaviour in the environment

Table 3. Selected environmental properties of difenoconazole.

| Parameter | Unit | Value | Remark | Reference |
|--|------|-------|--|-----------|
| Hydrolysis half-life (DT ₅₀) | [d] | > 30 | no significant hydrolysis (<10 %) was observed at pH 5, 7 and 9 after 30 days at 25 °C. | EC, 2006 |
| Photolysis half-life (DT ₅₀) | [d] | > 15 | no significant photolysis was observed after 15 days of irradiation | EC, 2006 |
| Readily biodegradable | | no | | EC, 2006 |
| Water/sediment systems (DT _{50, system}) | [d] | 315 | geometric mean of two systems | EC, 2006 |
| Relevant metabolites | | | CGA 205375 max. 4.9% in pond system (days 32 and 127), max. 11.6-11.4% in river system (days 90-183) | EC, 2006 |

3.1.4 Bioconcentration and biomagnification

An overview of the bioaccumulation data for difenoconazole is given in Table 4. Detailed bioaccumulation data for difenoconazole are tabulated in Appendix 1.

Table 4. Overview of bioaccumulation data for difenoconazole.

| Parameter | Unit | Value | Remark | Reference |
|------------|---------|-------|-----------------------------------|-----------|
| BCF (fish) | [L/kg] | 330 | whole fish | EC, 2006 |
| BMF | [kg/kg] | 1 | default value for BCF < 2000 L/kg | |

3.1.5 Human toxicological threshold limits and carcinogenicity

Difenoconazole has a (proposed) R22 classification (EC, 2006). The ADI is 0.01 mg.kg_{bw}/d (EC, 2006), based on a 2-year combined chronic toxicity/carcinogenicity study in rat with an NOAEL of 1.0 mg.kg_{bw}/d and an assessment factor of 100. In view of the lack of genotoxicity and the observation of liver adenomas/carcinomas only in mice and only at concentrations at which toxicity was observed, the substance is considered not likely to pose a carcinogenic risk to humans (EC, 2006).

3.2 Trigger values

This section reports on the trigger values for ERLwater derivation (as demanded in WFD framework).

Table 5. Difenoconazole: collected properties for comparison to MPC triggers.

| Parameter | Value | Unit | Method/Source | Derived at section |
|-------------------------------|------------|---------------------|--------------------------------------|--------------------|
| Log $K_{p,\text{susp-water}}$ | 2.58 | [-] | $K_{OC} \times f_{OC,\text{susp}}^1$ | K_{OC} : 3.1.2 |
| BCF | 330 | [L/kg] | | 3.1.4 |
| BMF | 1 | [kg/kg] | | 3.1.4 |
| Log K_{ow} | 4.36 | [-] | | 3.1.2 |
| R-phrases | R22, 50/53 | | | 3.1.5 |
| A1 value | 1.0 | [$\mu\text{g/L}$] | Total pesticides | |
| DW Standard | 0.1 | [$\mu\text{g/L}$] | General value for organic pesticides | |

¹ $f_{OC,\text{susp}} = 0.1 \text{ kg}_{OC}/\text{kg}_{\text{solid}}$ (EC, 2003).

- difenoconazole has a $\log K_{p,\text{susp-water}} < 3$; derivation of MPC_{sediment} is not triggered.
- difenoconazole has a $\log K_{p,\text{susp-water}} < 3$; expression of the MPC_{water} as MPC_{susp, water} is not required.
- difenoconazole has a BCF > 100 L/kg; assessment of secondary poisoning is triggered.
- difenoconazole has a (proposed) R22 classification and a BCF > 100 L/kg. Therefore, an MPC_{water} for human health via food (fish) consumption (MPC_{hh food, water}) should be derived.
- For difenoconazole, no specific A1 value or Drinking Water Standard is available from Council Directives 75/440, EEC and 98/83/EC, respectively. Therefore, the general Drinking Water Standard for organic pesticides applies.

3.3 Toxicity data and derivation of ERLs for water

3.3.1 MPC_{eco, water} and MPC_{eco, marine}

An overview of the selected freshwater toxicity data for difenoconazole is given in Table 6. Marine toxicity data are given in Table 7. Detailed toxicity data for difenoconazole are tabulated in Appendix 2.

Table 6. Difenoconazole: selected freshwater toxicity data for ERL derivation.

| Chronic ^a | | Acute ^a | |
|----------------------|-------------------|--------------------|-------------------|
| Taxonomic group | NOEC/EC10 (µg/L) | Taxonomic group | L(E)C50 (µg/L) |
| algae | 467 ^b | algae | 980 ^h |
| crustacea | 10 ^c | crustacea | 778 ⁱ |
| insecta | 34 ^d | pisces | 1300 |
| pisces | 59 ^e | pisces | 934 ^j |
| pisces | 7.6 ^f | macrophyta | 9900 ^k |
| macrophyta | 2500 ^g | | |

^a For detailed information see Appendix 2. Bold values are used for ERL derivation.

^b geometric mean of EC₁₀ 590 and 370 µg/L, preferred endpoint growth rate for *Scenedesmus subspicatus* (exposure 72h).

^c geometric mean of 5.6 and 18 µg/L, parameter reproduction for *Daphnia magna*

^d geometric mean of 15 and 75 µg/L, parameter emergence for *Chironomus riparius*

^e geometric mean of 23 and 150 µg/L for *Oncorhynchus mykiss*

^f most sensitive parameter larval weight for *Pimephales promelas*

^g in line with algae, the 14-days EC₅₀ for *Lemna gibba* is as considered acute

^h geometric mean of 3800 and 960 µg/L, preferred endpoint growth rate for *Scenedesmus subspicatus* (72h exposure).

ⁱ geometric mean of 770, 430, 830 940, and 1100 µg/L, parameter mortality/immobilisation for *D. magna*

^j geometric mean of 810, 1100, 650, 1800 and 910 µg/L for *O. mykiss*

^k in line with algae, the 14-days NOEC for *Lemna gibba* is as considered as chronic

Table 7. difenoconazole: selected marine toxicity data.

| Chronic ^a | | Acute ^a | |
|----------------------|------------------|--------------------|----------------|
| Taxonomic group | NOEC/EC10 (µg/L) | Taxonomic group | L(E)C50 (µg/L) |
| crustacea | | | 150 |
| fish | | | 950 |

^a For detailed information see Appendix 2.

3.3.1.1 Treatment of fresh- and saltwater toxicity data

ERLs for freshwater and marine waters should be derived separately. For pesticides, data can only be combined if it is possible to determine with high probability that marine organisms are not more sensitive than freshwater organisms (Lepper, 2005). For difenoconazole, there are only two toxicity data (acute only, base set not complete) and no marine ERLs can be derived.

3.3.1.2 Mesocosm and field studies

Not available.

3.3.1.3 Derivation of MPC_{eco, water} and MPC_{eco, marine}

The acute base set is complete. There are long-term NOECs from at least three species representing three trophic levels, and an assessment factor 10 is put on the lowest NOEC of 7.6 µg/L. The MPC_{eco, water} is 7.6 / 10 = 0.76 µg/L.

The MPC_{eco, marine} cannot be derived because not enough data are available.

3.3.2 MPC_{sp, water} and MPC_{sp, marine}

In view of the BCF \geq 100 L/kg, derivation of the MPC_{sp, water} and MPC_{sp, marine} is triggered. The available toxicity data for mammals and birds are presented in Appendix 3. In Table 8, the MPC_{oral} is

derived applying the appropriate assessment factors to the data. No default assessment factors are available for the teratogenicity studies, a factor of 300 is used.

The $MPC_{oral,min}$ is based on a 2-years NOAEL of 20 mg/kg_{diet} (rat) and an assessment factor of 30 (for the choice of $MPC_{oral,min}$, see table below and Appendix 3), resulting in an $MPC_{oral,min}$ of 0.67 mg/kg_{diet}.

Table 8. difenoconazole: selection of MPC_{oral}^a.

| Species | Exposure duration | Endpoint (mg/kg _{diet}) | Value | AF | MPC_{oral} (mg/kg _{diet}) |
|----------------|----------------------|-----------------------------------|-------|------------------|---------------------------------------|
| mallard duck | 18w | NOAEL | 625 | 30 | 21 |
| bobwhite quail | 5d | LC50 | 4760 | 3000 | 1.6 |
| bobwhite quail | 20w | NOAEL | 100 | 30 | 3.3 |
| mouse | 90d | NOAEL | 200 | 90 | 2.2 |
| dog | 6m | NOAEL | 1000 | 90 | 11 |
| mouse | 18m | NOAEL | 30 | 30 | 1.0 |
| rabbit | 12d (teratogenicity) | NOAEL | 833 | 300 ^b | 2.8 |
| rat | 9d (teratogenicity) | NOAEL | 400 | 300 ^b | 1.3 |
| rat | 28d | NOAEL | 1500 | 300 | 5.0 |
| rat | 90d | NOAEL | 250 | 90 | 2.8 |
| rat | 90d | NOAEL | 750 | 90 | 8.3 |
| rat | 2y | NOAEL | 20 | 30 | 0.67 |
| rat | 2-gen | NOAEL | 250 | 30 | 8.3 |

^a For detailed information see Appendix 3. Bold value is used for ERL derivation.

^b The assessment factor has been arbitrarily determined to be 300 from a worst case perspective. Both studies are teratology studies in which the a.i. has been applied by gavage during (a part of) gestation. Therefore the duration of exposure is < 28 days.

The $MPC_{sp,water}$ is $MPC_{oral,min} / (BCF \times BMF) = 0.67 / (330 \times 1) = 0.0020 \text{ mg/L} = 2.0 \text{ } \mu\text{g/L}$.

Because toxicity data for marine predators are generally not available, the $MPC_{oral,min}$ as derived above is used as a representative for the marine environment also. To account for the longer food chains in the marine environment, an additional biomagnification step is introduced (BMF_2). This factor is the same as given in Table 4. The $MPC_{sp,marine}$ is $0.67 / (330 \times 1 \times 1) = 0.0020 \text{ mg/L} = 2.0 \text{ } \mu\text{g/L}$.

3.3.3 $MPC_{hh,food,water}$

Derivation of the $MPC_{hh,food,water}$ is triggered (Table 5). The $MPC_{hh,food}$ is calculated from the ADI (0.01 mg/kg bw), a body weight of 70 kg and a daily fish consumption of 115 g, as $MPC_{hh,food} = 0.01 \times 0.1 \times 70 / 0.115 = 0.61 \text{ mg/kg}$ (Van Vlaardingen en Verbruggen, 2007). Subsequently the $MPC_{hh,food,water}$ is calculated according to $MPC_{hh,food,water} = 0.61 / (BCF_{fish} \times BMF_1) = 0.61 / (330 \times 1) = 0.0019 \text{ mg/L} = 1.9 \text{ } \mu\text{g/L}$.

3.3.4 $MPC_{dw,water}$

The Drinking Water Standard is 0.1 $\mu\text{g/L}$. Thus, the $MPC_{dw,water}$ is also 0.1 $\mu\text{g/L}$.

3.3.5 Selection of the MPC_{water} and MPC_{marine}

The lowest MPC value should be selected as the general MPC. The lowest value of the routes included (see Section 2.3.1) is the $MPC_{eco,water}$. The MPC_{water} is 0.76 $\mu\text{g/L}$.

No MPC_{marine} can be selected due to the insufficient amount of data.

3.3.6 MAC_{eco}

3.3.6.1 MAC_{eco, water}

Difenoconazole has a potential to bioaccumulate, the mode of action is non-specific and interspecies variation is low. Therefore, an assessment factor of 100 is applied on the lowest short-term LC₅₀ of 778 µg/L, yielding MAC_{eco, water} of 778 / 100 = 7.8 µg/L.

3.3.6.2 MAC_{eco, marine}

No MAC_{eco, marine} can be derived due to the insufficient amount of data..

3.3.7 SRC_{eco}

There are more than three NOECs available for at least three trophic levels including algae, *Daphnia* and fish. The SRC_{eco} is derived as the geometric mean of the freshwater chronic toxicity values, which is 75 µg/L.

3.4 Toxicity data and derivation of ERLs for sediment

The log $K_{p, \text{susp-water}}$ of difenoconazole is below the trigger value of 3; therefore, ERLs are not derived for sediment.

4 Conclusions

In this report, the risk limits Maximum Permissible Concentration (MPC), Maximum Acceptable Concentration for ecosystems (MAC_{eco}), and Serious Risk Concentration for ecosystems (SRC_{eco}) are derived for difenoconazole in water. No risk limits were derived for the marine compartment because not enough data were available. Derivation of ERLs for sediment was not triggered.

The ERLs that were obtained are summarised in the table below. The MPC values that were set for this compound until now, is also presented in this table for comparison reasons. It should be noted that this is an indicative MPC ('ad-hoc MTR'), derived using a different methodology and based on limited data.

Table 9. Derived MPC, MAC_{eco}, and SRC values for difenoconazole.

| ERL | Unit | MPC | MAC _{eco} | SRC _{eco} |
|-----------------------------|------|-------------------|--------------------|--------------------|
| Water, old ^a | µg/L | 0.011 | | |
| Water, new ^b | µg/L | 0.76 | 7.8 | 75 |
| Drinking water ^b | µg/L | 0.1 ^c | - | - |
| Marine | µg/L | n.d. ^d | n.d. ^d | - |

^a indicative MPC ('ad-hoc MTR'), source: Helpdesk Water
http://www.helpdeskwater.nl/emissiebeheer/normen_voor_het_zoeksysteem_normen/

^b The MPC_{dw, water} is reported as a separate value from the other MPC_{water} values (MPC_{eco, water}, MPC_{sp, water} or MPC_{hh food, water}). From these other MPC_{water} values (thus excluding the MPC_{dw, water}) the lowest one is selected as the 'overall' MPC_{water}.

^c provisional value pending the decision on implementation of the MPC_{dw, water} (see Section 2.3.1)

^d n.d. = not derived due to lack of data

References

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Appendix 1. Information on bioconcentration

Table A1.1 Bioconcentration data for difenoconazole

| Species properties | A | Test type | Test compound | Purity | Test water | pH | T | Hardness | Exp. time | Exp. conc. [mg/l] | BCF type | BCF whole fish | Ri | Notes | Reference |
|---|---|-----------|---------------|--------|------------|----|---|----------|-----------|-------------------|----------|----------------|----|-------|-----------|
| Pisces <i>Lepomis macrochirus</i> | | | | | | | | | | | | | | | |

NOTES

1. Concentrations are measured using ^{14}C techniques. A steady state concentration in fish tissues was reached within 3 days of exposure and 97% depuration occurred within 14 days of transfer to clean water.

Appendix 2. Detailed aquatic toxicity data

Table A2.1. Acute toxicity of difenoconazole to freshwater organisms.

| Species properties | A | Test type | Test compound | Purity [%] | Test water | pH | T [°C] | Hardness CaCO ₃ [mg/L] | Exp. time | Criterion | Test endpoint | Value [mg/L] | Ri | Notes | Reference |
|--|---|-----------|---------------|------------|------------|---------|---------|-----------------------------------|----------------|----------------|---------------|--------------|----------|----------|-----------|
| Algae | | | | | | | | | | | | | | | |
| <i>Pseudokirchneriella subcapitata</i> | Y | S | formulation | 3.1 | 7.7-9.0 | 24-25 | 72 h | EC50 | growth rate | > 2.9 | 2 | 1 | EC, 2006 | | |
| <i>Pseudokirchneriella subcapitata</i> | Y | S | formulation | 3.1 | 7.7-9.0 | 24-25 | 72 h | EC50 | biomass | 1.80 | 2 | 2 | EC, 2006 | | |
| <i>Scenedesmus subspicatus</i> | Y | S | 91.8 | 7.2-9.3 | 23 | 72 h | EC50 | growth rate | 3.80 | 2 | 3 | EC, 2006 | | | |
| <i>Scenedesmus subspicatus</i> | Y | S | 91.8 | 7.2-9.3 | 23 | 72 h | EC50 | biomass | 1.20 | 2 | 4 | EC, 2006 | | | |
| <i>Scenedesmus subspicatus</i> | Y | S | 91.8 | 7.7-8.1 | 23 | 72 h | EC50 | growth rate | 4 | 5 | | | | | |
| <i>Scenedesmus subspicatus</i> | Y | S | 91.8 | 7.7-8.1 | 24 | 72 h | EC50 | biomass | 0.03 | 2 | 6 | EC, 2006 | | | |
| <i>Scenedesmus subspicatus</i> | N | S | formulation | 25 | 7.5-8.3 | 23 | 96 h | EC50 | growth rate | 2.20 | 2 | 7 | EC, 2006 | | |
| <i>Scenedesmus subspicatus</i> | N | S | formulation | 25 | 7.5-8.3 | 23 | 96 h | EC50 | biomass | 1.60 | 2 | 8 | EC, 2006 | | |
| <i>Scenedesmus subspicatus</i> | Y | S | formulation | 25 | 7.7-8.1 | 23 | 72 h | EC50 | growth rate | 4 | 9 | EC, 2006 | | | |
| <i>Scenedesmus subspicatus</i> | Y | S | formulation | 25 | 7.7-8.1 | 23 | 72 h | EC50 | biomass | 0.04 | 2 | 10 | EC, 2006 | | |
| <i>Scenedesmus subspicatus</i> | Y | S | formulation | 25.2 | 7.9-9.1 | 22-23 | 24 | EC50 | growth rate | 0.96 | 2 | 11 | EC, 2006 | | |
| <i>Scenedesmus subspicatus</i> | Y | S | formulation | 25.2 | 7.9-9.1 | 22-23 | 24 | EC50 | biomass | 0.29 | 2 | 12 | EC, 2006 | | |
| Crustacea | | | | | | | | | | | | | | | |
| <i>Daphnia magna</i> | Y | S | 96.1 | 8.1-8.3 | 20-22 | 225-275 | 48 h | LC50 | mortality | 0.77 | 2 | 13 | EC, 2006 | | |
| <i>Daphnia magna</i> | Y | S | formulation | 3.1 | 7.5-7.6 | 20 | 168 | 48 h | EC50 | immobilisation | 0.43 | 2 | 14 | EC, 2006 | |
| <i>Daphnia magna</i> | N | S | formulation | 25 | 7.4-7.5 | 20 | 48 h | EC50 | immobilisation | 0.83 | 2 | 15 | EC, 2006 | | |
| <i>Daphnia magna</i> | Y | S | formulation | 25 | 7.9-8.3 | 20 | 240 | 48 h | EC50 | immobilisation | 0.94 | 2 | 16 | EC, 2006 | |
| <i>Daphnia magna</i> | Y | S | formulation | 25.2 | 7.9-8.0 | 19-20 | 250 | 48 h | EC50 | immobilisation | 1.10 | 2 | 17 | EC, 2006 | |
| Macrophyta | | | | | | | | | | | | | | | |
| <i>Lemna gibba</i> | N | S | 96.1 | | 25 | | 14 d | EC50 | growth | 9.9 | 2 | 6,31 | EC, 2006 | | |
| Pisces | | | | | | | | | | | | | | | |
| <i>Lepomis macrochirus</i> | Y | S | a.s. | 96.1 | 7.0-7.5 | 22-23 | 40-45 | 96 h | LC50 | mortality | 1.30 | 2 | 18 | EC, 2006 | |
| <i>Oncorhynchus mykiss</i> | Y | S | a.s. | 96 | 6.9-7.6 | 12 | 46 | 96 h | LC50 | mortality | 0.81 | 2 | 20 | EC, 2006 | |
| <i>Oncorhynchus mykiss</i> | F | a.s. | 96.1 | 6.6-7.2 | 11-13 | 32-33 | 96 h | LC50 | mortality | 1.10 | 2 | 22 | EC, 2006 | | |
| <i>Oncorhynchus mykiss</i> | F | a.s. | formulation | 3.1 | 6.6-7.5 | 14 | 180 | 96 h | LC50 | mortality | 0.7 | 2 | 24 | EC, 2006 | |
| <i>Oncorhynchus mykiss</i> | Y | S | formulation | 25 | 7.9-8.2 | 17 | 200-240 | 96 h | LC50 | mortality | 0.65 | 2 | 26 | EC, 2006 | |
| <i>Oncorhynchus mykiss</i> | Y | S | formulation | 25 | 7.6-8.3 | 15 | 180 | 96 h | LC50 | mortality | 0.80 | 2 | 27 | EC, 2006 | |
| <i>Oncorhynchus mykiss</i> | S | S | formulation | 25.2 | 8.5-8.7 | 13 | 207 | 96 h | LC50 | mortality | 0.91 | 2 | 29 | EC, 2006 | |

NOTES

1 Formulation contains 30.6 g/L-1 EC50 exceeds top dose (extrapolated value notifier was 3.3 mg a.s./L). OECD Guideline 201 (1984).

2 Formulation contains 30.6 g a.s./L. OECD Guideline 201 (1984). The calculation of an EC50 according to this guideline is considered inappropriate.

3 OECD Guideline 201 (1984).

4 OECD Guideline 201 (1984). The calculation of an EC50 according to this guideline is considered inappropriate.

5 The notifier only submitted an EC50 (area under growth curve), see below. The RMS tried to recalculate an EC50 based on the raw data but concluded that this was not possible as the growth rate data did not fit into a probit model. Due to this the whole study is considered not useful for ERL derivation. OECD Guideline 201 (1984).

6 Not reliable as only an EC50 could be calculated and no EC50. OECD Guideline 201 (1984). The calculation of an EC50 according to this guideline is considered inappropriate.

7 Formulation contains 250 g a.s./L. OECD Guideline 201 (1984).

8 Formulation contains 250 g a.s./L. OECD Guideline 201 (1984). The calculation of an EC50 according to this guideline is considered inappropriate.

9 Formulation contains 250 g a.s./L. The notifier only submitted an EC50 based on the raw data as the formulation was considered representative for the proposed formulation. So far, i.e. being unable to recalculate a proper EC50 based on the raw data, the whole study is considered not useful for ERL derivation. OECD Guideline 201 (1984).

10 Formulation contains 250 g a.s./L. No EC50 available, therefore not useful for ERL derivation. Recalculation as in Grade 1993b is not an option as the RMS does not provide raw data on growth rate in summary DAR. OECD Guideline 201 (1984).

11 Formulation contains 252 g a.s./L. OECD Guideline 201 (1984).
12 Formulation contains 252 g a.s./L. OECD Guideline 201 (1984). The calculation of an EC50 according to this guideline is considered inappropriate.
13 No information on clinical effects, so no acute NOEC can be derived by evaluator. Guideline US EPA FIFRA 72-2.
14 Formulation with 30.6 g a.s./L. OECD 202.
15 Formulation with 250 g a.s./L. Study not used for DAR risk assessment due to lack of analytical verification. OECD 202 I (1984).
16 Formulation with 250 g a.s./L. OECD 202.
17 Formulation with 252 g a.s./L. OECD Guideline No. 202, 1984. US EPA OPPTS Test Guidelines 850.1010, 1996.
18 US EPA FIFRA 72-1.
19 US EPA FIFRA 72-1.
20 Not used for risk assessment by RMS due to partial analytical verification (only measurements at start test). However, the study is sufficient for ERL derivation in view of relative persistence in water (see DAR, fate and behaviour). RIVM evaluated this study in 1993 as less reliable, though useful for risk assessment. US EPA FIFRA 72-1.
21 Not used for derivation ERL as validity is 3. US EPA FIFRA 72-1.
22 US EPA FIFRA 72-1.
23 No NOEC could be derived. US EPA FIFRA 72-1.
24 Formulation with 30.6 g a.s./L. LC50 is based on geometric mean of mean measured concentrations. OECD 203 (1992).
25 Formulation with 30.6 g a.s./L. OECD 203 (1992).
26 Formulation with 250 g a.s./L. LC50 is based on mean measured concentrations. OECD 203 (1984).
27 Formulation with 250 g a.s./L. LC50 is based on nominal concentrations. OECD 203 (1984).
28 Formulation with 250 g a.s./L. OECD 203 (1984).
29 Formulation was used with 252 g a.s./L. LC50 based on mg product/L, recalculated to a.s. via density of 1.0129 kg/L. OECD 203 (1992).
30 Formulation was used with 252 g a.s./L. LC50 based on mg product/L, recalculated to a.s. via density of 1.0129 kg/L. OECD 203 (1992).
31 14 days is chronic, but in line with algae, the EC50 is treated as acute, the NOEC as chronic

Table A2.2. Chronic toxicity of difenoconazole to freshwater organisms.

| Species | Species properties | A | Test type | Test compound | Purity [%] | Test water | pH | T [°C] | Hardness CaCO ₃ [mg/L] | Exp. time | Criterion | Test endpoint | Value [mg/L] | Ri | Notes | Reference |
|--------------------------------|--------------------|------|------------------|------------------|------------|------------|--------------|-----------------------------|-----------------------------------|-----------|-----------|---------------|--------------|----|-------|-----------|
| Algae | | | | | | | | | | | | | | | | |
| <i>Scenedesmus subspicatus</i> | Y S | 91.8 | 7.2-9.3 | 23 | 72 h | EC10 | growth rate | 0.59 | 2 | 12 | EC, 2006 | | | | | |
| <i>Scenedesmus subspicatus</i> | N S | 25 | 7.5-8.3 | 23 | 96 h | EC10 | growth rate | 1.10 | 2 | 12 | EC, 2006 | | | | | |
| <i>Scenedesmus subspicatus</i> | Y S | 25.2 | 7.9-9.1 | 22-23 | 72 h | EC10 | growth rate | 0.37 | 2 | 12 | EC, 2006 | | | | | |
| <i>Scenedesmus subspicatus</i> | Y S | 91.8 | 7.7-8.1 | 24 | 72 h | NOEC | growth rate | 0.0086 | 3 | 1 | EC, 2006 | | | | | |
| Crustacea | | | | | | | | | | | | | | | | |
| <i>Daphnia magna</i> | Y F | 96.1 | 8.1-8.3 | 20 | 206-275 | 21 d | NOEC | reproduction/length F0 | 0.0056 | 2 | 2 | EC, 2006 | | | | |
| <i>Daphnia magna</i> | N R | 25 | 7.8-8.2 | 21 | 21 d | NOEC | reproduction | 0.0180 | 2 | 3 | EC, 2006 | | | | | |
| Insecta | | | | | | | | | | | | | | | | |
| <i>Chironomus riparius</i> | larvae, 2-3 d old | Y S | 91 | Elindt M4 medium | 7.7 | 240 | NOEC | emergence, development rate | 0.0150 | 2 | 4 | EC, 2006 | | | | |
| <i>Chironomus riparius</i> | Y S | 25.5 | 8.4-9.9 | 20 | 244 | 28 d | NOEC | emergence rate | 0.0750 | 2 | 5 | EC, 2006 | | | | |
| Macrophyta | | | | | | | | | | | | | | | | |
| <i>Lemna gibba</i> | N S | 96.1 | Elindt M4 medium | 7.7 | 25 | 14 d | NOEC | growth | 2.5 | 2 | 7 | EC, 2006 | | | | |
| Pisces | | | | | | | | | | | | | | | | |
| <i>Oncorhynchus mykiss</i> | juv. 1.26 g; 48 mm | Y F | 91.8 | 7.8-8.3 | 15-16 | 150-164 | 21 d | NOEC | growth, feeding | 0.0230 | 2 | 8 | EC, 2006 | | | |
| <i>Oncorhynchus mykiss</i> | juveniles | Y R | 25 | 7.3-8.5 | 15-17 | 21 d | NOEC | growth, feeding | 0.1500 | 2 | 9 | EC, 2006 | | | | |
| <i>Pimephales promelas</i> | embryos and larvae | Y F | 96.1 | 6.6-7.2 | 24 | 30-31 | 34 | NOEC | larvae weight | 0.0076 | 2 | 10 | EC, 2006 | | | |
| <i>Pimephales promelas</i> | embryos and larvae | Y F | 95 | 7.0-7.7 | 25 | 26-28 | 68 | NOEC | larvae length | 0.0037 | 2 | 11 | EC, 2006 | | | |

NOTES

- 1 The notifier only submitted an Ebc50 (area under growth curve), see below. The RMS tried to recalculate an Erc50 based on the raw data but concluded that this was not possible as the growth rate data did not fit into a probit model. Due to this the whole study is considered not useful for ERL derivation. OECD Guideline 201 (1984).
- 2 US EPA FIFRA 72-4.
- 3 The formulation contained 250 mg a.s./L OECD 202 II (1984).
- 4 The NOEC is based on mean measured concentrations in the water phase. No measurements in the sediment. Sediment-spiked test. ASTM E1706 (1995). Sediment in accordance with OECD 207.
- 5 The NOEC is based on mean measured concentrations in the water phase. No measurements in the sediment. Formulation with 255 g a.s./L. Water-spiked test. BBA/IVIA ring-test protocol (1994).
- 6 US EPA FIFRA 122-2.
- 7 US EPA FIFRA 122-2.
- 8 OECD 204 (1984). Recoveries of a.i. during test: 40-69%. NOEC based on mean measured concentrations.
- 9 Formulation with 250 g a.s./L OECD 204 (1984). Recoveries of a.i. during test: 86-116%. NOEC based on nominal concentrations.
- 10 US EPA FIFRA 72-4.
- 11 US EPA FIFRA 72-4.
- 12 Recalculated conform RIVM methodology.

Table A2.1. Acute toxicity of difenoconazole (marine water).

| Species | Species properties | A | Test type | Test compound | Purity [%] | Test water | pH | T [°C] | Salinity [%] | Exp. time | Criterion | Test endpoint | Value [mg/L] | Ri | Notes | Reference |
|------------------------------|-------------------------|---|-----------|---------------|------------|------------|-------|--------|--------------|-----------|------------------|---------------|--------------|----|----------|-----------|
| Crustacea | | | | | | | | | | | | | | | | |
| <i>Mysidopsis bahia</i> | ≤ 24 h | Y | F | a.s. | 95 | 7.9-8.1 | 23-25 | 31-32 | 96 h | LC50 | mortality | 0.15 | 2 | 1 | EC, 2006 | |
| Mollusca | | | | | | | | | | | | | | | | |
| <i>Crassostrea virginica</i> | mean valve height 40 mm | Y | F | a.s. | 95 | 7.7-7.9 | 19-20 | 32-34 | 96 h | EC50 | shell deposition | > 0.30 | 3 | 2 | EC, 2006 | |
| Pisces | | | | | | | | | | | | | | | | |
| <i>Cyprinodon variegatus</i> | juv: 0.003 g; 6.5 mm | A | S | a.s. | 96.1 | 7.7-8.2 | 21-22 | 20 | 96 h | LC50 | mortality | 0.82 | 2 | 3 | EC, 2006 | |
| <i>Cyprinodon variegatus</i> | juv: 0.3 g; 28 mm | A | F | a.s. | 96 | 7.6-7.9 | 22 | 31-32 | 96 h | LC50 | mortality | 1.10 | 2 | 4 | EC, 2006 | |

NOTES

1 No information on clinical effects, so no acute NOEC can be derived by evaluator. US EPA FIFRA 72-3.

2 NOEC originally reported as 0.21 mg a.s./L, but not acknowledged by RMS in view of high variabilities of clinical effect at submortal concentrations. EC50 by RMS based on < 50% shell deposition at top-dose of 0.3 mg a.s./L. US EPA FIFRA 72-3.

3 Brackish test water. US EPA FIFRA 72-3.

4 Brackish water. US EPA FIFRA 72-3.

Appendix 3. Detailed bird and mammal toxicity data

Table A3.1. Toxicity of difenoconazole to birds and mammals.

| Species | Species properties | Purity | Application route | Exp. time | Criterion | Test endpoint | Value | Value | Ri | Notes | Reference |
|--------------|------------------------------|-----------------------------|-------------------|---------------------------------|-----------|---|--------|-------|----|----------|-----------|
| mallard duck | ducklings | 96.1 | diet | 5d | LC50 | mortality | > 5000 | 2 | | EC, 2006 | |
| mallard duck | 34w old | 91.1 | diet | 18w | NOAEL | reproduction and body weight | 625 | 2 | | EC, 2006 | |
| bobwhite | 14d old | 95.2 | diet | 5d | LC50 | mortality | 4760 | 2 | | EC, 2006 | |
| quail | 28w old | 94.3 | diet | 20w | NOAEL | reproduction and body weight of 1-d old hatching | 100 | 2 | | EC, 2006 | |
| rat | SPF-Wistar (outbred KFM-Han) | ≥ 95 | diet | 28d | NOAEL | body weight, carcass weight, organ weight | 1500 | 2 | | EC, 2006 | |
| rat | CRL:CD (SD) ® rats | 94.5 | diet | 90d | NOAEL | body weight, heart weight, carcass weight, food consumption | 250 | 2 | | EC, 2006 | |
| rat | CD-1® (ICR) mice | 94.5 | diet | 90d | NOAEL | body weight gain | 750 | 2 | | EC, 2006 | |
| mouse | purebred beagles | 96.1 | diet | 6m | NOAEL | body weight gain | 200 | 2 | 1 | EC, 2006 | |
| dog | Sprague Dawley® CRL: CD rats | 106 | diet | 2y | NOAEL | food consumption | 1000 | 2 | | EC, 2006 | |
| rat | CD-1® (ICR) mice | 94.5 (w 1-20), 95 (w 21-80) | diet | 18m | NOAEL | body weight and body weight gain | 20 | 2 | | EC, 2006 | |
| mouse | purebred beagles | 96.1 | 1y | | NOAEL | body weight gain (males) | 30 | 2 | | EC, 2006 | |
| dog | 37-38d old rats | 97.4 | two generations | | NOAEL | food consumption | ≥ 1500 | 2 | | EC, 2006 | |
| rat | New Zealand White rabbits | 95.7 | by gavage | d 7-19 of presumed gestation | NOAEL | (parental) body weight, food consumption, abortion, foetal resorption | 250 | 2 | 1 | EC, 2006 | |
| rat | Crl:COBS®CD®(SD) BR rats | | by gavage | d 6 to 15 of presumed gestation | NOAEL | (maternal) body weight gain, food consumption | 833 | 2 | | EC, 2006 | |

NOTES

1 rabbit teratogenicity study by gavage; NOAEL food recalculated by mg/kgbw/d times the conversion factor of 33.3

2 rat teratogenicity study by gavage; NOAEL food recalculated by mg/kgbw/d times the conversion factor of 20

Appendix 4. References used in the appendices

EC. 2006. Draft Assessment report difenoconazole. Updated December 2006. RMS Sweden.

RIVM

National Institute
for Public Health
and the Environment

P.O. Box 1
3720 BA Bilthoven
The Netherlands
www.rivm.com