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ERA-AQUA version 2.0, technical description and manual

A decision support system for the Environmental Risk Assessment of veterinary medicines applied in pond AQUAculture

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A decision support system for the Environmental Risk Assessment of veterinary medicines applied in pond AQUAculture

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Abstract

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Veterinary medicinal products are applied in aquaculture production for treating and preventing diseases in the cultured species. Veterinary medicines may enter the environment by effluent discharges, posing a potential risk for surrounding aquatic ecosystems. Furthermore, human health and the trade of the aquaculture produce can be negatively affected by the presence of residues of veterinary medicines in the cultured organisms. The ERA-AQUA Decision Support System was developed to estimate risks of veterinary medicinal products applied in pond aquaculture for the targeted produce, surrounding aquatic ecosystems, consumers and trade. The risk assessment is expressed by risk quotients, which are calculated by dividing the predicted exposure concentration by the predicted no effect concentration calculated for each endpoint. This report provides a mathematical description of the processes incorporated in the ERA-AQUA Decision Support System and a user's manual.

Keywords: Aquaculture, Veterinary medicines, Risk assessment, Aquatic ecosystems, Human health.

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Summary

Veterinary medicinal products are applied worldwide in aquaculture production for treating and preventing bacterial diseases and parasitic infestations in the cultured species. On the one hand, aquaculture medicinal products can be considered as a powerful tool for improving the health status of the cultured species and increasing the productivity of the aquaculture farms. However, on the other hand, some veterinary medicines might pose a risk for the targeted aquaculture animals when they are not used according to recommendations. Veterinary medicines may enter the environment through the continuous or intermittent discharge of aquaculture effluents, posing a potential risk for the biodiversity and functioning of surrounding aquatic ecosystems. In addition to this, human health and trade may be negatively affected by the presence of residues of veterinary medicines in the aquaculture produce. The ERA-AQUA Decision Support System was developed to estimate risks posed by the use of veterinary medicines in pond aquaculture production systems for the targeted produce, non-target aquatic organisms (acute and chronic), consumers, and the trade of the aquaculture produce. For all risk assessments an exposure as well as an effect assessment is performed following a conservative approach. In the exposure assessment, concentrations of the aquaculture drug are calculated in the pond water, in the targeted produce and in the effluent discharge point of the adjacent aquatic ecosystems by mass balance equations. The effect assessment consists of determining safe concentrations for the different compartments, and is based on the use of safety factors applied to toxicity data or food safety standards. The risk assessment is then performed by following a risk quotient approach, by dividing the predicted exposure concentration by the predicted no effect concentration in the compartment under study. When the predicted exposure concentration exceeds the predicted no effect concentration it is indicated by the DSS. The ERA-AQUA DSS Version 2.0 is incorporated in a Graphical User Interface in Microsoft EXCEL and is freely available at www.era-aqua.wur.nl. This report provides a mathematical description of the processes incorporated into the ERA-AQUA DSS and a user's manual.

1 Introduction

The intensification of aquaculture practices worldwide has led to the introduction of a wide range of veterinary medicines for treating and preventing bacterial diseases and parasitic infestations in the cultured species (e.g. Asia: Rico et al., 2012; Brazil: Rebouças et al., 2011; Mexico: Lyle-Fritch et al., 2006). On the one hand, aquaculture medicinal products can be considered as a powerful tool for improving the health status of the cultured species and increasing the productivity of the aquaculture farms. However, on the other hand, some veterinary medicines might pose a risk for the targeted aquaculture species when they are not used according to recommendations since they can induce mortalities or reduce the growth rates in the cultured organisms. Veterinary medicines may enter the environment through the continuous or intermittent discharge of (untreated) aquaculture effluents (e.g. Le and Munksgaard, 2004), posing a potential risk for the biodiversity and natural functioning of surrounding aquatic ecosystems. In addition to this, human health and trade may be negatively affected by the presence of residues of veterinary medicines in the aquaculture produce, since they might result in potential side-effects on consumers (e.g. development of antimicrobial resistant bacteria in humans, toxicity, allergy)(Moats and Medina 1996) and rejections of aquaculture products in national and international food safety controls (Albabouch et al., 2005; Love et al., 2011).

The ERA-AQUA Decision Support System was developed to assess the risks posed by the use of veterinary medicines in pond aquaculture production systems for i) the targeted produce, ii) adjacent aquatic ecosystems receiving aquaculture effluents, iii) consumers, and iv) trade. For all risk assessments an exposure as well as an effect assessment is performed following a conservative approach. In the exposure assessment, concentrations of the aquaculture drug in the pond water, the targeted produce and peak and time weighted average concentrations in the effluent discharge point of the adjacent aquatic ecosystems are calculated. The effect assessment consists of determining 'safe' concentrations for the different compartments and is based on the use of safety factors applied to laboratory toxicity data or food safety standards. The risk assessment is then performed by following a risk quotient approach, by dividing the predicted exposure concentration by the predicted 'safe' concentration in the compartment under study. If risk quotients are smaller than 1, the estimated exposure is smaller than the 'safe' concentration and there is not exceedance of the calculated safe concentration (i.e., not expected risk). If risk quotients are larger than 1, the estimated exposure exceeds the calculated 'safe' concentration and it is indicated by the model. If risk quotients are larger than a certain cut-off value (10 in this model), the model indicates a large exceedance of the calculated safe concentration (i.e., expected risks). The ERA-AQUA Decision Support System can be used for i) the identification of veterinary medicines that may result in a loss of the productivity of the aquaculture pond and/or may pose a risk for external aquatic ecosystems, human health and the trade of the aquaculture produce, given certain dosages and aquaculture practices, ii) the assessment of the influence of different chemical application schemes and aquaculture management practices on the environmental impacts of aquaculture production, and iii) the design of chemical and biological monitoring studies and other higher-tier risk assessment studies. This report provides a mathematical description of the processes incorporated into the ERA-AQUA Decision Support System and a user's manual.

2 Exposure assessment

The ERA-AQUA Decision Support System predicts the concentration dynamics of veterinary medicines in four different compartments: pond water, pond sediment, the cultured species and the water layer of the watercourse receiving effluent discharges by considering fifteen different drug transfer or dissipation processes (Figure 1). The drug fate and distribution modeling is based on mass balance equations.

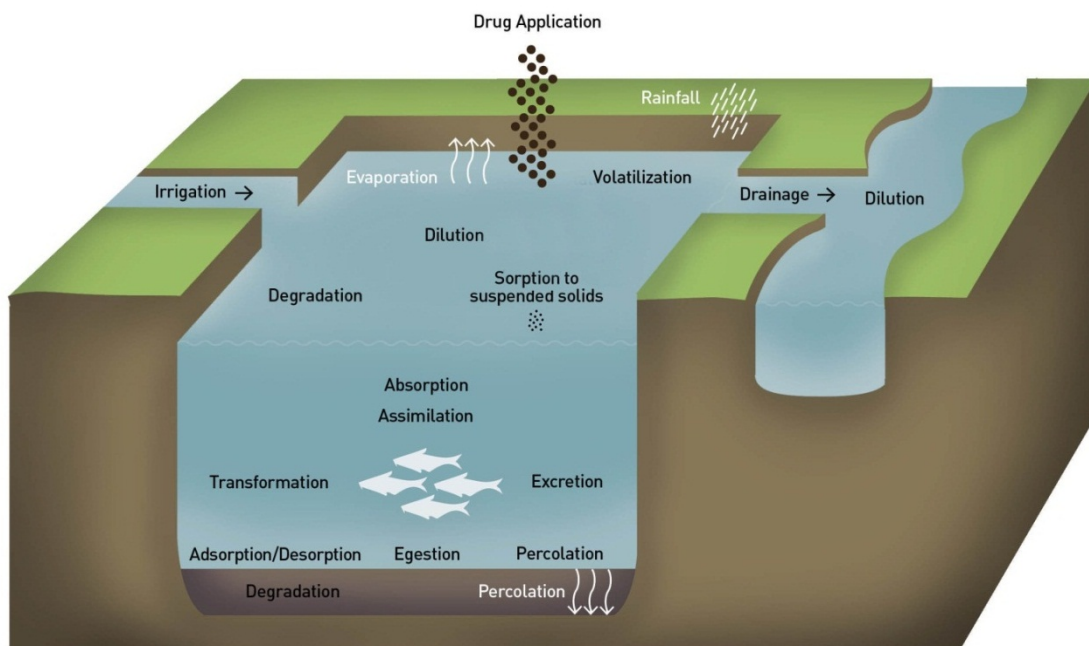


Figure 1

Processes modeled by the ERA-AQUA Decision Support System.

The peak concentration in the pond water during the simulation period is used to assess potential risks for the targeted produce. The concentration of the drug in the cultured organisms at the moment of harvest is estimated in order to assess potential risks for consumers and trade. For assessing acute risks for aquatic organisms, the peak concentration in the effluent mixing zone of the watercourse receiving the pond effluent discharge is calculated. For assessing chronic risks for aquatic organisms, time weighted average concentrations in the mixing zone are calculated. All these concentrations are calculated following a conservative approach and trying as far as possible to limit the number of input parameters required for the simulation. For example, the fraction of the drug that is applied mixed with feed and is not ingested by the cultured species is assumed to be dissolved instantaneously in the pond water; the dissolved drug in the pond water introduced by the fraction of non-eaten feed or by bath treatment applications is assumed to reach an instantaneous sorption equilibrium with the suspended solids; and effluent discharges occurring on the same day the drug is applied are assumed to start 2h after the application of the drug.

The following steps are performed by the model in order to calculate concentrations of the drug in the different compartments mentioned above:

- a. Calculation of the mass transfer and dissipation rate coefficients.

- b. Calculation of the water balance and the cultured species mass balance in the aquaculture pond.
- c. Calculation of predicted pond water, pond sediment and cultured species concentrations.
- d. Calculation of the predicted peak pond water concentration.
- e. Calculation of the predicted concentration in the cultured species at harvest.
- f. Calculation of predicted peak and time weighted average drug concentrations in the watercourse.

These six steps will be described in the following sections.

2.1 Calculation of the drug mass transfer and dissipation rate coefficients

First, the drug mass transfer and dissipation rate coefficients used by the model for the calculation of the drug concentration dynamics in the water, sediment and cultured species compartments are calculated. In this section, the equations used by the model for the calculation of the volatilization coefficient, the degradation rate coefficient in water and sediment, the sediment desorption rate, and the uptake and elimination rate constants of the drug in the cultured species are described.

2.1.1 Volatilization coefficient

The volatilization coefficient is calculated according to the method developed by Mackay and Leinonen (1975):

$$k_{volatilization} = \left[\frac{1}{k_L^{CO_2} \cdot \sqrt{\frac{M_{CO_2}}{M}}} + \frac{1}{K_H \cdot k_G^{H_2O} \cdot \sqrt{\frac{M_{H_2O}}{M}}} \right]^{-1} \quad (\text{Eq. 1})$$

with,

$k_{volatilization}$ = mass transfer coefficient of the substance from water to atmosphere at ambient temperature (m/d)

M = relative molecular mass of the substance (g/mol)

M_{CO_2} = relative molecular mass of CO₂ (constant parameter = 44 g/mol)

M_{H_2O} = relative molecular mass of H₂O (constant parameter = 18 g/mol)

$k_L^{CO_2}$ = mass transfer coefficient of CO₂ in water (Liss and Slater, 1974 estimated a $k_L^{CO_2}$ of 4.8 m/d = constant parameter)

$k_G^{H_2O}$ = mass transfer coefficient of H₂O in air (Liss and Slater, 1974 estimated a $k_G^{H_2O}$ of 720 m/d = constant parameter)

K_H = dimensionless Henry coefficient of the substance (-)

The Henry coefficient is calculated according to the following equation:

$$K_H = \frac{VP(T) \cdot 0.001 \cdot M}{R \cdot (273.15 + T) \cdot SOL(T)} \quad (\text{Eq. 2})$$

(Adriaanse 1996) with,

K_H = dimensionless Henry coefficient of the substance (-)

$VP(T)$ = saturated vapor pressure of the substance at ambient temperature (mPa)

M = relative molecular mass of the substance (g/mol)

R = universal gas constant (constant parameter \approx 8.3144 J/mol K)

T = average ambient temperature in the modeled scenario (°C)

$SOL(T)$ = solubility of the substance in water at ambient temperature (mg/L)

0.001 = correction factor to convert from mPa to Pa

The saturated vapor pressure of the substance at a certain temperature is calculated by using the Van't Hoff equation:

$$VP(T) = VP(T_{ref}) \cdot \exp\left[-\frac{\Delta H_p}{R} \cdot \left(\frac{1}{273.15 + T} - \frac{1}{273.15 + T_{refVP}}\right)\right] \quad (\text{Eq. 3})$$

(Van den Berg and Boesten, 1998) with,

$VP(T)$ = saturated vapor pressure of the substance at ambient temperature (mPa)

T = average ambient temperature in the modeled scenario (°C)

T_{refVP} = reference temperature at which $VP(T_{ref})$ was determined (°C)

$VP(T_{ref})$ = saturated vapor pressure of the substance at reference temperature (mPa)

ΔH_p = enthalpy of vaporization (default value: pesticides and antibiotics = 97000 J/mol, disinfectants: 31700 J/mol)

R = universal gas constant (constant parameter ≈ 8.3144 J/mol K)

For many compounds the enthalpy of vaporization is available. However, when it is not available, the average enthalpy of vaporization of 97 kJ/mol is recommended for pesticides and antibiotics. This value is based on the study of Smit et al. (1997) on sixteen pesticides (ranging from 58 to 146 kJ/mol, average: 95 kJ/mol) and the values showed in Appendix I for twelve antibiotics commonly used in Asian pond aquaculture (Rico et al., 2012) collected from the literature (ranging from 74 to 145, average 99.5 kJ/mol). Disinfectants are characterized by a lower enthalpy of vaporization. For disinfectants the default value of 31.7 kJ/mol is proposed based on enthalpies of vaporization for some disinfectants typically used in Asian aquaculture (Rico et al. 2012) (Appendix I).

The solubility of the compound at the ambient temperature in the modeled scenario is calculated by using the Van't Hoff equation:

$$SOL(T) = SOL(T_{ref}) \cdot \exp\left[-\frac{\Delta H_{SOL}}{R} \cdot \left(\frac{1}{273.15 + T} - \frac{1}{273.15 + T_{refSOL}}\right)\right] \quad (\text{Eq. 4})$$

(Van den Berg and Boesten 1998) with,

$SOL(T)$ = solubility of the substance in water at ambient temperature (mg/L)

$SOL(T_{ref})$ = solubility of the substance in water at reference temperature (mg/L)

ΔH_{SOL} = enthalpy of dissolution (default value = 25000 J/mol)

R = universal gas constant (constant parameter ≈ 8.3144 J/mol · K)

T = average ambient temperature in the modeled scenario (°C)

T_{refSOL} = reference temperature at which $SOL(T_{ref})$ was determined (°C)

The enthalpy of dissolution (ΔH_{SOL}) is substance dependent. Jain et al. (2000) calculated the enthalpy of dissolution for the antibiotics ampicillin (23.2 kJ/mol) and amoxicillin (26.3 kJ/mol) at pH=7 and 37.15 °C. Zhang and Wang (2008) calculated the enthalpy of dissolution for six quinolone antibiotics and found values ranging between 8.2 and 36.4 kJ/mol at 25 °C (average: 20.9 kJ/mol). Bowman and Sans (1985) found a range of -17 to 156 kJ/mol for 29 pesticides, with an average of 27 kJ/mol. Enthalpies of dissolution for disinfectants used in Asian aquaculture (Rico et al., 2012) collected from different literatures and databases are shown in Appendix I, with an average value of 25.3 kJ/mol. Given the similarity of the average values reported for antibiotics, pesticides and disinfectants, a default value of 25 kJ/mol is proposed when the enthalpy of dissolution for the compound under study is not available.

2.1.2 Degradation rate in water

The degradation rate is a function of the half dissipation time of the compound on the compartment under study, which reflects the overall degradation rate due to microbial degradation, hydrolysis and photolysis, and is calculated by:

$$k_w(T_{refw}) = \frac{\ln(2)}{DT50_{water}} \quad (\text{Eq. 5})$$

with,

$k_w(T_{refw})$ = first-order degradation rate coefficient of the substance in water at reference temperature (1/d)

$DT50_{water}$ = half-life degradation of the substance in water at reference temperature (d)

In many cases available $DT50_{water}$ values are derived from a water-sediment study. In such cases these values reflect hydrolysis and photolysis, but are additionally influenced by partitioning processes between the water and the sediment phase, and dissipation processes occurring in the sediment such as microbial degradation or formation of bound residues. Therefore, it is preferable to use $DT50_{water}$ values derived from hydrolysis and photolysis experiments in water without sediment in order to get a more realistic estimation.

The degradation rate coefficient calculated at reference temperature can be adjusted to the ambient temperature by using the Arrhenius equation:

$$k_w(T) = k_w(T_{refw}) \cdot \exp\left[\frac{E}{R \cdot (273.15 + T_{refw}) \cdot (273.15 + T)} \cdot (T - T_{refw})\right] \quad (\text{Eq. 6})$$

with,

$k_w(T)$ = first-order degradation rate coefficient of the substance in water at ambient temperature (1/d)

$k_w(T_{refw})$ = first-order degradation rate coefficient of the substance in water at reference temperature (1/d)

E = molar Arrhenius activation energy (default value = 65400 J/mol)

R = universal gas constant (constant parameter ≈ 8.3144 J/mol · K)

T = average ambient temperature in the modeled scenario (°C)

T_{refw} = reference temperature at which $DT50_{water}$ was determined (°C)

The European panel on Plant Protection Products and Residues derived a median molar Arrhenius activation energy of 65.4 kJ/mol based on data for 53 different pesticides (Barceló et al., 2007). Loftin et al. (2008) estimated the Arrhenius activation energy for three antibiotics (i.e., chlortetracycline, oxytetracycline, tetracycline) at different pH values ranging between 2 to 11 in water under laboratory conditions. Considering only the Arrhenius activation energies for those pHs that are likely to be found in aquaculture ponds (5-9), an average value of 71.6 kJ/mol ($n = 8$, $SD = 19.4$) was calculated. Given the similarity between the values reported for pesticides and for antibiotics by Loftin et al. (2008), and the lack of values reported for other compounds such as disinfectants, an Arrhenius activation energy of 65.4 kJ/mol as proposed by Barceló et al. (2007) is given by the model as default value.

2.1.3 Degradation rate in sediment

The degradation rate constant in sediment is assumed to follow a first order kinetics and is calculated by the following equation:

$$k_s(T_{refs}) = \frac{\ln(2)}{DT50_{sediment}} \quad (\text{Eq. 7})$$

with,

$k_s(T_{refs})$ = first-order degradation rate coefficient of the substance in sediment at reference temperature (1/d)

$DT50_{sediment}$ = half-life degradation of the substance in sediment at reference temperature (d)

The $DT50_{\text{sediment}}$ is not easily available for all the compounds. When it is not available, the half-life degradation in soil calculated under aerobic conditions can be used to approximate the $DT50_{\text{sediment}}$. The degradation rate coefficient in sediment can be adjusted to the scenario's ambient temperature according to the Arrhenius equation:

$$k_s(T) = k_s(T_{\text{refs}}) \cdot \exp\left[\frac{E}{R \cdot (273.15 + T_{\text{refs}}) \cdot (273.15 + T)} \cdot (T - T_{\text{refs}})\right] \quad (\text{Eq. 8})$$

with,

$k_s(T)$ = first-order degradation rate coefficient of the substance in sediment at ambient temperature (1/d)
 $k_s(T_{\text{refs}})$ = first-order degradation rate coefficient of the substance in sediment at reference temperature (1/d)
 E = molar Arrhenius activation energy (default value = 65400 J/mol)
 R = universal gas constant (constant parameter ≈ 8.3144 J/mol·K)
 T = average ambient temperature in the modeled scenario (°C)
 T_{refs} = reference temperature at which $DT50_{\text{sediment}}$ was determined (°C)

2.1.4 Desorption rate from sediment

The desorption rate of the substance from the sediment is assumed to follow first-order kinetics and is calculated according to the hindered diffusion model described by Birdwell et al. (2007):

$$k_{\text{desorption}} = \frac{D_w(T)}{\varphi^{-1/3} \cdot \left(1 + \frac{\rho}{\varphi} \cdot K_{oc} \cdot f_{oc}\right) \cdot l^2} \quad (\text{Eq. 9})$$

with,

$k_{\text{desorption}}$ = first-order desorption rate coefficient (1/d)
 $D_w(T)$ = aqueous diffusivity of the substance in water at the scenario temperature (cm²/d)
 φ = sediment porosity (v/v)
 ρ = sediment bulk density (kg/L)
 K_{oc} = sorption coefficient of the substance on organic carbon (L/kg)
 f_{oc} = mass fraction of organic carbon in sediment (-)
 l = characteristic length scale (constant value = 0.05 cm)

Hayduk and Laudie (1974) demonstrated a clear relationship between the molar mass and the aqueous diffusivity (calculated at 25°C) for several molecules of different size. According to the relation established by Hayduk and Laudie (1974), the aqueous diffusivity of different compounds at 25°C can be estimated by:

$$D_w(T_{\text{refw}}) = \frac{23.33}{M^{0.71}} \quad (\text{Eq. 10})$$

with,

$D_w(T_{\text{refw}})$ = aqueous diffusivity of the substance in water at 25°C (cm²/d)
 M = relative molecular mass of the substance (g/mol)

The aqueous diffusivity of chemicals is temperature dependent, mainly because the viscosity of water depends on the temperature. The diffusion coefficient for a specific temperature is corrected with the following equation:

$$D_w(T) = [1 + 0.02571 \cdot (T - T_{\text{refDw}})] \cdot D_w(T_{\text{refDw}}) \quad (\text{Eq. 11})$$

(Tucker and Nelken, 1982; Leistra et al., 2001) with,

$D_w(T)$ = aqueous diffusivity of the substance in water at the scenario temperature (cm²/d)

T = average ambient temperature in the modeled scenario (°C)

$T_{ref,DW}$ = reference temperature at which $D_w(T_{ref,DW})$ was determined (constant value = 25°C)

$D_w(T_{ref,W})$ = aqueous diffusivity of the chemical in water at the reference temperature (25°C)

The fraction of the volume of voids over the total volume (ϕ) depends upon the texture of the sediment. Egna and Boyd (1997) proposed a series of porosity values for different sediment textures in aquaculture ponds (Table 1). These porosity values are recommended based the sediment texture classification of the pond scenario under study when no porosity data is available.

Table 1

Theoretical porosity values for aquaculture pond sediments based on the sediment texture (Source: Egna and Boyd, 1997).

Sediment texture	Porosity (v/v)
Sand	0.38
Sandy loam	0.43
Loam	0.47
Clay loam	0.49
Silty clay	0.51
Clay	0.53

The fraction of organic carbon of the sediment can be estimated from the fraction of organic matter of the sediment according to the following relation:

$$f_{oc} = 0.58 \cdot f_{om} \quad (\text{Eq. 12})$$

(FOCUS 2001) with,

f_{oc} = mass fraction of organic carbon in sediment (-)

f_{om} = mass fraction of organic matter in sediment (-)

The characteristic length scale (l) is assumed to be intrinsically related to the particle size of the sediment. Average particle radius or diameter appears in some models but the validity of its use might be questionable given the fact that size distributions of sediment particles are often non-Gaussian and particle size has not always been correlated to a specific desorption behaviour (see Birdwell et al., 2007 and references therein). In the present model, an average characteristic length scale of 0.05 cm is employed as default value as used in Birdwell et al. (2007).

2.1.5 Calculation of drug uptake and elimination rate constants for the cultured organisms

First-order uptake and elimination rate constants of the substance in the cultured species are calculated according to the equations described by Hendriks et al. (2001), which are part of the OMEGA model (Optimal Modeling for Ecotoxicological Applications). The drug influx and efflux rate constants are calculated based on the octanol-water partition coefficient of the substance under study and considering a series of resistances in water and lipid layers and flow delays. The present model considers drug uptake by the cultured species as a function of the absorption from water and assimilation from food. Total elimination of the drug in the cultured

species takes into account four different processes: physicochemical transport with water, elimination via faeces, metabolic transformation in the cultured species and dilution by growth (the last process not being a real elimination process). The calculation of the rate constants for each of the uptake and elimination processes is described below. For a more detailed description on the calculation of the uptake and elimination rate constants the reader is referred to Hendriks et al. (2001) and Hauck et al. (2011).

The rate constant for absorption from water is calculated by:

$$k_{absorption} = \frac{w^{-\kappa}}{\rho_{H_2O} + \frac{\rho_{CH_2}}{k_{ow}} + \frac{1}{\gamma_0}} \quad (\text{Eq. 13})$$

(Hendriks et al., 2001) with,

$k_{absorption}$ = absorption rate constant of the substance in the cultured species (L/kg · d)

w = organism weight (kg)

κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)

ρ_{H_2O} = partial water layer diffusion resistance to and from water (d · kg^{-κ}) (Default value = 0.0068; Hauck et al., 2011)

ρ_{CH_2} = lipid layer permeation resistance (d · kg^{-κ}) (Default value = 97; Hauck et al., 2011)

k_{ow} = octanol/water partition coefficient of the substance (-)

γ_0 = water absorption-excretion coefficient (kg^κ/d) (Default value = 4200; Hauck et al., 2011)

The metabolic rate constants can be correlated to the organism weight (w) by applying an exponent κ derived by surface/volume relationships (Hendriks et al., 2001 and references therein). A rate exponent of 0.25, as used by Hendriks et al. (2001), is used in the present model as default value. Default values for the partial water layer diffusion resistance to and from water, the lipid layer permeation resistance and the water-absorption excretion coefficient are based on the Maximum Likelihood Estimations made by Hauck et al. (2011) for fish.

The rate constant for assimilation from food is calculated by:

$$k_{assimilation} = \frac{p_1}{1-p_1} \cdot \frac{1}{\rho_{CH_2, food} \cdot (k_{ow}^{-1}) + 1} \cdot \frac{w^{-\kappa}}{\rho_{H_2O, food} + \frac{\rho_{CH_2}}{q_{T,c} \cdot k_{ow}} + \frac{1}{\rho_{CH_2, food} \cdot k_{ow} \cdot (1-p_1) \cdot q_{T,c} \cdot \gamma_1}} \quad (\text{Eq.14})$$

(Hendriks et al., 2001) with,

$k_{assimilation}$ = drug assimilation rate constant in the cultured species ($\frac{\mu\text{g} \cdot \text{kg cultured species}^{-1}}{\mu\text{g} \cdot \text{kg food}^{-1}} \cdot 1/d$)

p_1 = fraction of ingested food assimilated (kg cultured species/kg food)

$\rho_{CH_2, food}$ = lipid fraction of food (-)

k_{ow} = octanol/water partition coefficient of the substance (-)

w = organism weight (kg)

κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)

$\rho_{H_2O, food}$ = partial water layer diffusion resistance to and from food (d · kg^{-κ}) (Default value = 0.0002; Hauck et al., 2011)

ρ_{CH_2} = lipid layer permeation resistance (d · kg^{-κ}) (Default value = 97; Hauck et al., 2011)

$q_{T,c}$ = temperature correction factor (kg/kg) (Constant value = 1, for cold-blooded organisms)

γ_1 = food ingestion coefficient (kg^κ/d)

The default value for the partial water layer diffusion resistance to and from food is chosen according to the Maximum Likelihood Estimations made by Hauck et al. (2011) for fish. The temperature correction factor is set to 1 since the majority of the cultured aquatic species are cold-blooded.

The fraction of ingested food assimilated is calculated from the Feed Conversion Ratio (FCR; mass of eaten feed divided by the body mass gain) of the administered feed for the cultured species.

$$p_1 = \frac{1}{FCR} \quad (\text{Eq. 15})$$

p_1 = fraction of ingested food assimilated (kg cultured species/kg food)

FCR = feed conversion ratio (kg food/kg cultured species)

The food ingestion coefficient is calculated by Eq. 16 assuming that the amount of feed made available to the cultured species by the farmers (i.e., specific feeding rate) will vary depending on the cultured organism's weight during the culture cycle according to its feeding requirements. In addition, Eq. 16 assumes that the fraction of ingested feed (FE) is constant during the culture cycle and the concentration of the drug in feed and/or water does not influence the food ingestion rate of the cultured organisms.

$$\gamma_1 = SFR \cdot w_{SFR}^{\kappa} \cdot FE \quad (\text{Eq. 16})$$

with,

γ_1 = food ingestion coefficient (kg^κ/d)

SFR = daily specific feeding rate (kg food/kg cultured species · 1/d)

w_{SFR} = organism's weight at which SFR was determined (kg)

κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)

FE = fraction of eaten feed (-)

The rate constant for elimination via excretion with water is calculated by:

$$k_{excretion} = \frac{1}{p_{CH_2} \cdot (k_{ow} - 1) + 1} \cdot \frac{w^{-\kappa}}{\rho_{H_2O} + \frac{\rho_{CH_2}}{k_{ow}} + \frac{1}{\gamma_0}} \quad (\text{Eq. 17})$$

(Hendriks et al., 2001) with,

$k_{excretion}$ = drug excretion rate constant (1/d)

p_{CH_2} = lipid fraction of cultured organisms (-)

k_{ow} = octanol/water partition coefficient of the substance (-)

w = organism weight (kg)

κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)

ρ_{H_2O} = partial water layer diffusion resistance to and from water (d · kg^{-κ}) (Default value = 0.0068; Hauck et al., 2011)

ρ_{CH_2} = lipid layer permeation resistance (d · kg^{-κ}) (Default value = 97; Hauck et al., 2011)

γ_0 = water absorption-excretion coefficient (kg^κ/d) (Default value = 4200; Hauck et al., 2011)

The rate constant for elimination via food egestion in the cultured species is calculated by:

$$k_{egestion} = \frac{1}{p_{CH_2} \cdot (k_{ow} - 1) + 1} \cdot \frac{w^{-\kappa}}{\rho_{H_2O, food} + \frac{\rho_{CH_2}}{q_{T.c} \cdot k_{ow}} + \frac{1}{p_{CH_2, food} \cdot k_{ow} \cdot (1 - p_1) \cdot q_{T.c} \cdot \gamma_1}} \quad (\text{Eq. 18})$$

(Hendriks et al., 2001) with,

$k_{egestion}$ = drug egestion rate constant (1/d)

p_{CH_2} = lipid fraction of the cultured organism (-)

k_{ow} = octanol/water partition coefficient of the substance (-)

w = organism weight (kg)

κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al. 2001)

$\rho_{H2O,food}$ = partial water layer diffusion resistance to and from food ($d \cdot kg^{-\kappa}$) (Default value = 0.0002; Hauck et al., 2011)

ρ_{CH2} = lipid layer permeation resistance ($d \cdot kg^{-\kappa}$) (Default value = 97; Hauck et al., 2011)

$q_{T,c}$ = temperature correction factor (kg/kg) (Constant value = 1, for cold-blooded organisms)

$\rho_{CH2, food}$ = lipid fraction of food (-)

ρ_I = fraction of ingested food assimilated (kg cultured species/ kg food)

γ_I = food ingestion coefficient (kg^κ/d)

The biotransformation rate constant of the drug in the cultured species is calculated according to Van der Linde et al. (2001) from the difference between the experimentally derived total elimination rate constant and the estimated minimum elimination (Eq. 19). The estimated minimum elimination is calculated as the sum of the excretion with water, the egestion and the dilution with biomass (growth) rate constants.

$$k_{transformation} = k_{elimination(M,T)} - (k_{excretion} + k_{egestion} + k_{cs-growth}) \quad (\text{Eq. 19})$$

with,

$k_{transformation}$ = drug biotransformation rate constant (1/d)

$k_{elimination(M,T)}$ = normalized total drug elimination rate constant in the cultured species (1/d)

$k_{excretion}$ = drug excretion rate constant (1/d)

$k_{egestion}$ = drug egestion rate constant (1/d)

$k_{cs-growth}$ = cultured species growth rate constant (1/d)

For the cases in which the $k_{elimination(M,T)}$ is lower than the sum of the calculated $k_{excretion}$, $k_{egestion}$ and $k_{cs-growth}$ the model considers $k_{transformation} = 0$, assuming that the drug elimination in the cultured species is only driven by excretion, egestion and dilution processes. Biological half-life values of veterinary medicines in aquaculture species calculated in pharmacokinetic studies can be retrieved from the freely available Phish-Pharm database (Reimschuessel et al., 2005). The species, the weight of the studied individuals, the temperature and characteristics of the experimental media, as well as the drug application scheme, are frequently reported. When using such biological half-life values, it is important to select values reported for the specific modeled drug and species treated with similar dosages and similar environmental conditions to the modeled scenario.

The first-order total drug elimination rate constant is calculated with the more available biological half-life of the drug in the cultured species by:

$$k_{elimination(Mref,Tref)} = \frac{\ln(2)}{BioT_{1/2(Mref,Tref)}} \quad (\text{Eq. 20})$$

with,

$k_{elimination(Mref,Tref)}$ = total drug elimination rate constant in the cultured species calculated for a specific cultured species mass and temperature (1/d)

$BioT_{1/2(Mref,Tref)}$ = biological half-life of the drug in the cultured species calculated for a reference cultured species mass and temperature (d)

The Eq. 21 is applied to correct the total drug elimination rate in the cultured species for the weight of the cultured organisms and the temperature in the modeled scenario:

$$k_{elimination(M,T)} = k_{elimination(Mref,Tref)} \cdot \left(\frac{w}{w_{ref,BioT_{1/2}}}\right)^{-\kappa} \cdot \exp(0.01 \cdot (T - T_{ref,BioT_{1/2}})) \quad (\text{Eq. 21})$$

(Arnot et al. 2009) with,

$k_{elimination(M,T)}$ = normalized total drug elimination rate constant in the cultured species (1/d)

$k_{elimination (Mref, Tref)}$ = total drug elimination rate in the cultured species calculated for a specific cultured species mass and temperature (1/d)

w = organism weight (kg)

$w_{ref, BioT_{1/2}(Mref, Tref)}$ = organism's weight at which $BioT_{1/2}(Mref, Tref)$ was determined (kg)

T = average ambient temperature in the modeled scenario (°C)

$T_{ref, BioT_{1/2}}$ = temperature at which $BioT_{1/2}(Mref, Tref)$ was determined (°C)

The cultured species growth rate or biomass dilution rate constant is calculated according to Hendriks et al. (2001) by:

$$k_{cs-growth} = q_{T:c} \cdot \gamma_2 \cdot w^{-\kappa} \quad (\text{Eq. 22})$$

with,

$k_{cs-growth}$ = cultured species growth rate constant (1/d)

$q_{T:c}$ = temperature correction factor (kg/kg) (Constant value = 1, for cold-blooded organisms)

γ_2 = biomass production coefficient (kg $^\kappa$ /d)

w = organism weight (kg)

κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)

Assuming that the drug exposure will not influence the growth rate in the cultured species, the biomass production coefficient due to organism's growth is calculated by:

$$\gamma_2 = \gamma_1 \cdot p_1 \quad (\text{Eq. 23})$$

with,

γ_2 = biomass production coefficient (kg $^\kappa$ /d)

γ_1 = food ingestion coefficient (kg $^\kappa$ /d)

p_1 = fraction of ingested food assimilated (kg cultured species/kg food)

2.2 Calculation of the water balance and the cultured species mass balance

2.2.1 Water balance

The water balance in the aquaculture pond is calculated taking into account water inputs from irrigation (water supply) and precipitation, and water outputs due to drainage (effluent discharge), percolation and evaporation according to the following equation:

$$A \cdot \frac{\partial h_{pond-water}}{\partial t} = A \cdot (IRRI + RAIN - DRAIN - PERC - EVAP) \quad (\text{Eq. 24})$$

with,

A = area of the pond (m²)

$h_{pond-water}$ = depth of water layer in the aquaculture pond (m)

$IRRI$ = average daily water supply rate (m/d)

$RAIN$ = average daily rainfall rate (m/d)

$DRAIN$ = average daily water drainage rate (m/d)

$PERC$ = average daily water percolation rate (m/d)

$EVAP$ = average daily evaporation rate (m/d)

2.2.2 Cultured species mass balance

The cultured species mass balance is a function of the total number of cultured organisms in the aquaculture pond and the growth of the cultured organisms. The total number of cultured organisms in the aquaculture pond changes according to the given mortality rate for the simulation period:

$$\frac{\partial N_{ind}}{\partial t} = -k_{mortality} \cdot N_{ind_o} \quad (\text{Eq. 25})$$

with,

N_{ind} = number of individuals in the aquaculture pond (-)

$k_{mortality}$ = mortality rate constant (1/d)

N_{ind_o} = number of individuals in the aquaculture pond at the start of the simulation period (-)

The number of cultured organisms at the start of the simulation period is calculated by:

$$N_{ind_o} = \frac{\rho_{cs} \cdot A}{w_o} \quad (\text{Eq. 26})$$

with,

N_{ind_o} = number of individuals in the aquaculture pond at the start of the simulation period (-)

ρ_{cs} = cultured species density at the start of the simulation period (kg/m²)

A = area of the pond (m²)

w_o = organism weight at the start of the simulation period (kg)

The mortality rate constant is assumed to be constant during the culture cycle and is calculated by dividing the mortality fraction by the length of the culture cycle:

$$k_{mortality} = \frac{MORT}{Harvest - Stock} \quad (\text{Eq. 27})$$

with,

$k_{mortality}$ = mortality rate constant (1/d)

$MORT$ = mortality fraction during the culture cycle (-)

$Harvest$ = Planned harvest day after the start of the simulation period (d)

$Stock$ = Planned cultured species stocking day after the start of the simulation period (d)

The average individual growth of the cultured organisms is calculated according to the Von Bertalanffy's asymptotic growth model (Von Bertalanffy 1938) by:

$$\frac{\partial w}{\partial t} = 3 \cdot k_{cs-growth} \cdot w \cdot \left[\left(\frac{w_{max}}{w} \right)^{\frac{1}{3}} - 1 \right] \quad (\text{Eq. 28})$$

(Kooijman 2000) with,

$k_{cs-growth}$ = cultured species growth rate constant (1/d)

w = organism weight (kg)

w_{max} = maximum organism weight (kg)

The asymptotic weight or theoretical maximum organism weight can be defined as the average weight that an individual (i.e., cultured organisms) would reach during its lifespan in optimal health conditions.

Finally, combining Eq. 25 and 28, the variation of the cultured species mass in the aquaculture pond is calculated by:

$$\frac{\partial M_{cs}}{\partial t} = \frac{\partial(N_{ind} \cdot w)}{\partial t} = \frac{\partial N_{ind}}{\partial t} \cdot w + \frac{\partial w}{\partial t} \cdot N_{ind} + \frac{\partial N_{ind}}{\partial t} \cdot \frac{\partial w}{\partial t} = (-k_{mortality} \cdot N_{ind_o} \cdot w) + \left(3 \cdot k_{cs-growth} \cdot w \left[\left(\frac{w_{max}}{w} \right)^{\frac{1}{3}} - 1 \right] \cdot N_{ind} \right) + \left(-k_{mortality} \cdot N_{ind_o} \cdot 3 \cdot k_{cs-growth} \cdot w \cdot \left[\left(\frac{w_{max}}{w} \right)^{\frac{1}{3}} - 1 \right] \right) \quad (\text{Eq. 29})$$

with,

M_{CS} = cultured species mass (kg)

$k_{mortality}$ = mortality rate constant (1/d)

N_{ind_o} = number of individuals in the aquaculture pond at the start of the simulation period (-)

w = organism weight (kg)

$k_{cs-growth}$ = cultured species growth rate constant (1/d)

w_{max} = maximum organism weight (kg)

N_{ind} = number of individuals in the aquaculture pond (-)

2.3 Calculation of drug concentration dynamics in the aquaculture pond

In this section the mass balance equations used by the model for the calculation of pond water, pond sediment and cultured species concentrations are described.

2.3.1 Calculation of concentration dynamics in the pond water layer

The pond water layer is composed by water and suspended solids and, hence, the total concentration of the drug in the water layer is calculated as the sum of the fraction of the drug that is dissolved in water and the fraction that is sorbed to suspended solids according to the following equation:

$$PWC_{total} = PWC_{diss} + PWC_{ss} \quad (\text{Eq. 30})$$

with,

PWC_{total} = predicted total drug concentration in the pond's water (mg/L)

PWC_{diss} = predicted dissolved pond water concentration (mg/L)

PWC_{ss} = predicted concentration of the drug in the pond water sorbed to suspended solids (mg/L)

The model assumes a sorption equilibrium of the drug between suspended solids and water. This equilibrium is based on the sorption coefficient of the drug on organic matter. In this way, the ratio between the dissolved and sorbed concentrations is re-equilibrated when the water or suspended solids concentrations are changed. The ratio between the dissolved and the sorbed fraction of the compound to suspended solids can be expressed as:

$$K_{om} \cdot m_{om,ss} = \frac{PWC_{ss}}{ss \cdot PWC_{diss}} \quad (\text{Eq. 31})$$

with,

K_{om} = sorption coefficient on organic matter (L/kg)

$m_{om,ss}$ = mass fraction of organic matter in suspended solids (g/g)
 PWC_{ss} = predicted concentration of the drug in the pond water sorbed to suspended solids (mg/L)
 ss = mass concentration of suspended solids in pond water (kg/L)
 PWC_{diss} = predicted dissolved pond water concentration (mg/L)

The sorption coefficient on organic matter (K_{om}) is calculated from the more available sorption coefficient to organic carbon (K_{oc}) by:

$$K_{om} = 0.58 \cdot K_{oc} \quad (\text{Eq. 32})$$

(FOCUS 2001) with,

K_{om} = sorption coefficient on organic matter (L/kg)

K_{oc} = sorption coefficient on organic carbon (L/kg)

The model assumes that the drug can be applied either by bath treatment (applied directly to the pond water surface) or by in-feed treatment (mixed with feed). For substances applied in bath treatments, a complete mixing of the substance in the pond water right after application is assumed. For drugs applied mixed with feed, the fraction of the substance that is not ingested by the cultured species is modeled separately to the fraction of the substance that is ingested by the cultured species. The dissolution of drugs from uneaten feed in the pond water is thought to be a complex process influenced by the type of feed used (e.g. pelleted *vs* extruded), surface-to-volume ratio of food particles, binding agents and methods, water temperature, and solubility of the drug (Xu et al., 1994; Duis et al., 1995; Rigos et al., 1999). Duis et al. (1995) found losses of several antibiotics (oxytetracycline, amoxicillin, trimethoprim/suphamethoxazole) from oil-coated fish-feed pellets ranging from 41.6 to 67.3% after 15 minutes of immersion, denoting that this is a quick process. In the present model a conservative approach was used, assuming instantaneous dissolution of the portion of applied drug in uneaten feed after application. The dissolution of drugs from feed before consumption by the cultured species was not considered in the present model. The drug concentration in the aquaculture pond water after application is calculated according to Eq. 33 assuming that there is only one single drug application per day:

$$PWC_{total} = (1 - DA) \cdot D + \frac{DA \cdot D \cdot M_{CS} \cdot (1 - FE)}{A \cdot h_{pond-water} \cdot 1000} \quad (\text{Eq. 33})$$

with,

PWC_{total} = predicted total drug concentration in the pond's water (mg/L)

DA = drug administration method ($DA=0$ for bath treatments; $DA=1$ for drugs mixed with feed)

D = individual drug dose applied (mg/L for drugs applied in bath treatments or mg/kg cultured species for drugs applied mixed with feed)

M_{CS} = cultured species mass (kg)

FE = fraction of eaten feed (-)

A = area of the pond (m^2)

$h_{pond-water}$ = depth of water layer in the aquaculture pond (m)

1000 = correction factor to convert from m^3 to L

The momentary dissolved predicted pond water concentration after drug application is calculated after the redistribution of the drug between the water and suspended solids by:

$$PWC_{diss} = \frac{c^*}{1 + ss \cdot m_{om,ss} \cdot K_{om}} \quad (\text{Eq. 34})$$

(Adriaanse, 1996) with,

PWC_{diss} = predicted dissolved pond water concentration (mg/L)
 c^* = total drug concentration in the pond after drug application (mg/L)
 ss = mass concentration of suspended solids in pond water (kg/L)
 $m_{om,ss}$ = mass fraction of organic matter in suspended solids (g/g)
 K_{om} = sorption coefficient on organic matter (L/kg)

Besides the equilibrium between the dissolved and sorbed fraction to suspended solids, the variation of the dissolved drug concentration in the water layer of the aquaculture pond over time is considered to be influenced by the sorption/desorption of drug to the sediment compartment, the drug excretion from the cultured species by physico-chemical transport with water, the addition of drug through irrigation water, the transport out of the pond via drainage and percolation, the volatilization of the drug from pond water to the atmosphere, the degradation of the drug in pond water due to biochemical and photochemical processes and the cultured species drug absorption from water. The equation for the mass balance in the pond water compartment is given by:

$$\frac{\partial M_{pond\ water\ diss}}{\partial t} = + M_{adsorption/desorption} + M_{excretion} + M_{irrigation} - M_{drainage} - M_{percolation} - M_{volatilization} - M_{degradation} - M_{absorption} \quad (\text{Eq. 35})$$

with,

$M_{pond\ water\ diss}$ = dissolved drug mass in the pond water (g)
 $M_{adsorption/desorption}$ = drug mass addition/loss rate by sorption/desorption to sediment (g/d)
 $M_{excretion}$ = drug mass addition rate due to excretion by the cultured species (g/d)
 $M_{irrigation}$ = drug mass addition rate by irrigation water (g/d)
 $M_{drainage}$ = drug mass loss rate by effluent discharge (g/d)
 $M_{percolation}$ = drug mass loss rate by percolation (g/d)
 $M_{volatilization}$ = drug mass loss rate by volatilization (g/d)
 $M_{degradation}$ = drug mass loss rate due to biochemical and photochemical degradation processes (g/d)
 $M_{absorption}$ = drug mass loss rate due to absorption from water by the cultured species (g/d)

The change in the pond water concentration due to drug sorption/desorption is calculated according to the following equation:

$$M_{adsorption/desorption} = - A \cdot h_{pond-sediment} \cdot \rho \cdot k_{desorption} \cdot (k_d \cdot PWC_{diss} - PSC) \quad (\text{Eq. 36})$$

with,

$M_{adsorption/desorption}$ = drug addition/loss from the water phase due to sorption/desorption to sediment (g/d)
 A = area of the pond (m²)
 $h_{pond-sediment}$ = depth of the top sediment layer in the aquaculture pond (m)
 ρ = sediment bulk density (kg/L)
 $k_{desorption}$ = first-order desorption rate coefficient (1/d)
 k_d = sediment/water partitioning coefficient of the substance (L/kg)
 PWC_{diss} = predicted dissolved pond water concentration (mg/L)
 PSC = predicted pond sediment concentration (mg/kg)

The sediment-water partition coefficient is calculated according to the following equation:

$$k_d = 0.58 \cdot f_{om} \cdot K_{oc} \quad (\text{Eq. 37})$$

(Karickhoff 1981) with,

k_d = sediment/water partitioning coefficient of the substance (L/kg)
 f_{om} = mass fraction of organic matter in sediment (-)
 K_{oc} = sorption coefficient of the substance on organic carbon (L/kg)

The rate of drug mass elimination from the cultured species by physicochemical transport with water is calculated according to:

$$M_{excretion} = k_{excretion} \cdot PCC \cdot 10^{-6} \cdot M_{CS} \quad (\text{Eq. 38})$$

with,

$M_{excretion}$ = drug mass addition rate due to excretion by the cultured species (g/d)
 $k_{excretion}$ = drug excretion rate constant (1/d)
 PCC = predicted cultured species concentration ($\mu\text{g}/\text{kg}$)
 10^{-6} = correction factor to convert from $\mu\text{g}/\text{kg}$ to g/kg
 M_{CS} = cultured species mass (kg)

The rate of drug mass entering the aquaculture pond with irrigation water is calculated by:

$$M_{irrigation} = A \cdot IRRI \cdot C_{IRRI} \quad (\text{Eq. 39})$$

with,

$M_{irrigation}$ = drug mass addition rate with irrigation water (g/d)
 A = area of the pond (m^2)
 $IRRI$ = average daily water supply rate (m/d)
 C_{IRRI} = dissolved drug concentration in the irrigation water (mg/L)

The rate of drug mass leaving the pond water compartment due to the effluent discharge is calculated by:

$$M_{drainage} = A \cdot DRAIN \cdot PWC_{diss} \quad (\text{Eq. 40})$$

with,

$M_{drainage}$ = drug mass loss rate by effluent discharge (g/d)
 A = area of the pond (m^2)
 $DRAIN$ = average daily water drainage rate (m/d)
 PWC_{diss} = predicted dissolved pond water concentration (mg/L)

The rate of drug transport by percolation from the pond water into the sediment is calculated by:

$$M_{percolation} = A \cdot PERC \cdot PWC_{diss} \quad (\text{Eq. 41})$$

with,

$M_{percolation}$ = drug mass loss rate by percolation (g/d)
 A = area of the pond (m^2)
 $PERC$ = average daily water percolation rate (m/d)
 PWC_{diss} = predicted dissolved pond water concentration (mg/L)

The drug mass loss rate due to volatilization is calculated by:

$$M_{volatilization} = A \cdot k_{volatilization} \cdot PWC_{diss} \quad (\text{Eq. 42})$$

with,

$M_{volatilization}$ = drug mass loss rate by volatilization (g/d)

A = area of the pond (m²)

$k_{volatilization}$ = mass transfer coefficient of the substance from water to atmosphere (m/d)

PWC_{diss} = predicted dissolved pond water concentration (mg/L)

The drug loss rate due to degradation takes into account photolysis and biochemical degradation processes. When the first-order degradation rate coefficient, $k_w(T_{refw})$, was calculated taking into account photolysis processes, the photolysis rate coefficient in water ($k_{photolysis}$) must be set to zero. It is important to use values of $k_{photolysis}$ calculated under similar radiation intensities to those of the scenario of study, especially for some antibiotics, which have been demonstrated to be largely degraded by photolytic processes in aquaculture ponds (Lai et al. 2009). The drug loss rate due to dissipation processes in the pond water is calculated by:

$$M_{degradation} = A \cdot h_{pond-water} \cdot (k_{photolysis} + k_w(T)) \cdot PWC_{diss} \quad (\text{Eq. 43})$$

with,

$M_{degradation}$ = drug mass loss rate due to biochemical and photochemical processes (g/d)

A = area of the pond (m²)

$h_{pond-water}$ = depth of water layer in the aquaculture pond (m)

$k_{photolysis}$ = first-order photolysis rate coefficient in water (1/d)

$k_w(T)$ = first-order degradation rate coefficient of the substance in water at ambient temperature (1/d)

PWC_{diss} = predicted dissolved pond water concentration (mg/L)

The drug loss rate due to absorption from the water layer by the cultured species is calculated by:

$$M_{absorption} = k_{absorption} \cdot PWC_{diss} \cdot 10^{-3} \cdot M_{CS} \quad (\text{Eq. 44})$$

with,

$M_{absorption}$ = drug mass absorption rate from water by the cultured species (g/d)

$k_{absorption}$ = drug absorption rate constant in the cultured species (L/kg · d)

PWC_{diss} = predicted dissolved pond water concentration (mg/L)

10^{-3} = correction factor to convert from mg/L to g/L

M_{CS} = cultured species mass (kg)

Finally, combining Eq. 36 and Eq. 38-44, the governing equation for the dissolved drug mass balance in the pond water reads:

$$A \cdot \frac{\partial(h_{pond-water} \cdot PWC_{diss})}{\partial t} = \left(A \cdot \frac{\partial h_{pond-water}}{\partial t} \cdot PWC_{diss} \right) + \left(A \cdot \frac{\partial PWC_{diss}}{\partial t} \cdot h_{pond-water} \right) + \left(A \cdot \frac{\partial h_{pond-water}}{\partial t} \cdot \frac{dPWC_{diss}}{dt} \right) = - A \cdot h_{pond-sediment} \cdot \rho \cdot k_{desorption} \cdot (k_d \cdot PWC_{diss} - PSC) + (k_{excretion} \cdot PCC \cdot 10^{-6} \cdot M_{CS}) + (A \cdot IRRI \cdot C_{IRRI}) - (A \cdot DRAIN \cdot PWC_{diss}) - (A \cdot PERC \cdot PWC_{diss}) - (A \cdot k_{volatilization} \cdot PWC_{diss}) - (A \cdot h_{pond-water} \cdot (k_{photolysis} + k_w(T)) \cdot PWC_{diss}) - (k_{absorption} \cdot PWC_{diss} \cdot 10^{-3} \cdot M_{CS}) \quad (\text{Eq. 45})$$

with,

A = area of the pond (m²)

$h_{pond-water}$ = depth of water layer in the aquaculture pond (m)

PWC_{diss} = predicted dissolved pond water concentration (mg/L)

$h_{pond-sediment}$ = depth of the top sediment layer in the aquaculture pond (m)

ρ = sediment bulk density (kg/L)

$k_{desorption}$ = first-order desorption rate coefficient (1/d)

k_d = sediment/water partitioning coefficient of the substance (L/kg)

PSC = predicted pond sediment concentration (mg/kg)
k_{excretion} = drug excretion rate constant (1/d)
PCC = predicted cultured species concentration (µg/kg)
 10^6 = correction factor to convert from µg/kg to mg/kg
M_{CS} = cultured species mass (kg)
IRRI = average daily water supply rate (m/d)
C_{IRRI} = dissolved drug concentration in the irrigation water (mg/L)
DRAIN = average daily water drainage rate (m/d)
PERC = average daily water percolation rate (m/d)
k_{volatilization} = mass transfer coefficient of the substance from water to atmosphere at ambient temperature (m/d)
k_{photolysis} = first-order photolysis rate coefficient in water (1/d)
k_{w(T)} = first-order degradation rate coefficient in water at ambient temperature (1/d)
k_{absorption} = drug absorption rate constant in the cultured species (L/kg · d)
 10^{-3} = correction factor to convert from mg/L to g/L

The mass of drug sorbed to suspended solids is influenced by the irrigation (i.e., potential entry of contaminated suspended solids and therefore adjustment of the equilibrium between dissolved and the sorbed fraction of the drug), and drainage (i.e., release of suspended solids through water discharges).

$$\frac{\partial M_{pond\ water\ ss}}{\partial t} = + M_{irrigation,ss} - M_{drainage,ss} \quad (\text{Eq. 46})$$

with,

M_{pond water ss} = mass of drug sorbed to suspended solids in the pond water (g)
M_{irrigation, ss} = drug mass input rate with suspended solids by irrigation (g/d)
M_{drainage, ss} = drug mass output rate with suspended solids by effluent discharge (g/d)

The variation in the mass of drug sorbed to suspended solids due to water irrigation is calculated by:

$$M_{irrigation,ss} = IRRI \cdot A \cdot ss \cdot C_{IRRI} \cdot K_{om} \cdot m_{om,ss} \quad (\text{Eq. 47})$$

with,

M_{irrigation,ss} = drug mass input rate with suspended solids by irrigation (g/d)
IRRI = average daily water supply rate (m/d)
A = area of the pond (m²)
ss = mass concentration of suspended solids in pond water (kg/L)
C_{IRRI} = dissolved drug concentration in the irrigation water (mg/L)
K_{om} = sorption coefficient on organic matter (L/kg)
m_{om,ss} = mass fraction of organic matter in suspended solids (g/g)

The variation in the mass of drug sorbed to suspended solids due to water drainage is calculated by:

$$M_{drainage,ss} = DRAIN \cdot A \cdot PWC_{ss} \quad (\text{Eq. 48})$$

with,

M_{drainage, ss} = drug mass output rate with suspended solids by effluent discharge (g/d)
DRAIN = average daily water drainage rate (m/d)
A = area of the pond (m²)
PWC_{ss} = predicted concentration of the drug in the pond water sorbed to suspended solids (mg/L)

Finally, combining Eq. 47 and 48, the governing equation for the drug mass sorbed to suspended solids reads:

$$A \cdot \frac{\partial(PWC_{ss} \cdot h_{pond-water})}{\partial t} = \left(A \cdot \frac{\partial PWC_{ss}}{\partial t} \cdot h_{pond-water} \right) + \left(A \cdot \frac{\partial h_{pond-water}}{\partial t} \cdot PWC_{ss} \right) + \left(A \cdot \frac{\partial h_{pond-water}}{\partial t} \cdot \frac{\partial PWC_{ss}}{\partial t} \right) = (IRRI \cdot A \cdot ss \cdot C_{IRRI} \cdot K_{om} \cdot m_{om,ss}) - (DRAIN \cdot A \cdot PWC_{ss}) \quad (\text{Eq. 49})$$

with,

A = area of the pond (m²)

PWC_{ss} = predicted concentration of the drug in the pond water sorbed to suspended solids (mg/L)

$h_{pond-water}$ = depth of water layer in the aquaculture pond (m)

$IRRI$ = average daily water supply rate (m/d)

ss = mass concentration of suspended solids in pond water (kg/L)

C_{IRRI} = dissolved drug concentration in the irrigation water (mg/L)

K_{om} = sorption coefficient on organic matter (L/kg)

$m_{om,ss}$ = mass fraction of organic matter in suspended solids (g/g)

$DRAIN$ = average daily water drainage rate (m/d)

2.3.2 Calculation of concentration dynamics in the pond sediment

The model allows the possibility to perform simulations with sediment (i.e., earthen ponds or concrete ponds with sediment layer) and without sediment (i.e., aquaculture tanks) as an additional compartment. For the simulations without sediment, the sediment depth is zero and the fraction of the drug egested by the cultured organisms is assumed to reach the water compartment. When the sediment compartment is included in the model calculations, drug concentrations in the top sediment layer are a function of the drug percolation, the drug deposition in the sediment through faeces, the drug degradation in sediment and the adsorption/desorption processes of the drug to and from the sediment to pond water. The equation for the mass balance in the pond sediment compartment is given by:

$$\frac{\partial M_{pond\ sediment}}{\partial t} = + M_{percolation} + M_{egestion} + M_{adsorption/desorption} - M_{degradation} \quad (\text{Eq. 50})$$

with,

$M_{pond\ sediment}$ = drug mass in pond sediment (g)

$M_{percolation}$ = drug mass addition/loss rate by percolation (g/d)

$M_{egestion}$ = drug mass addition rate due to egestion by the cultured species (g/d)

$M_{adsorption/desorption}$ = drug mass addition/loss rate due to sorption/desorption to sediment (g/d)

$M_{degradation}$ = drug mass loss rate due to degradation processes in the sediment (g/d)

The drug mass transfer from water to the top-layer of the sediment or the drug mass loss from the top-layer of the sediment due to water percolation are calculated according to Eq. 51 according to the water/sediment drug mass equilibrium.

$$M_{percolation} = A \cdot PERC \cdot (k_d \cdot PWC_{diss} - PSC) \quad (\text{Eq. 51})$$

with,

$M_{percolation}$ = drug mass addition rate by percolation (g/d)

A = area of the pond (m²)

$PERC$ = average water percolation rate (m/d)

PWC_{diss} = predicted dissolved pond water concentration (mg/L)
 k_d = sediment/water partitioning coefficient of the substance (L/kg)
 PSC = predicted pond sediment concentration (mg/kg)

The rate of the drug mass eliminated by egestion is calculated by summing the fraction of drug that has been assimilated by the cultured species and eliminated through faeces, and the fraction that has not been assimilated (Eq. 52). The latter fraction is assumed to be instantaneously released unaltered through faeces after ingestion. The rate of drug mass eliminated from the cultured species by faeces is assumed to be instantaneously settled into the pond sediment.

$$M_{egestion} = (k_{egestion} \cdot PCC \cdot 10^{-6} \cdot M_{CS}) + \left[\frac{DA \cdot D \cdot FE \cdot M_{CS}}{1000} \cdot \left(1 - k_{assimilation} \cdot \frac{1}{SFR \cdot \left(\frac{w}{w_{SFR}} \right)^{-\kappa}} \right) \right] \quad (\text{Eq. 52})$$

with,

$M_{egestion}$ = drug mass addition rate due to egestion by the cultured species (g/d)
 $k_{egestion}$ = drug egestion rate constant (1/d)
 PCC = predicted cultured species concentration ($\mu\text{g}/\text{kg}$)
 10^6 = correction factor to convert from $\mu\text{g}/\text{kg}$ to g/kg
 M_{CS} = cultured species mass (kg)
 DA = drug administration method ($DA=0$ for bath treatments; $DA=1$ for drugs mixed with feed)
 D = individual drug dose applied (mg/L for drugs applied in bath treatments or mg/kg cultured species for drugs applied mixed with feed)
 FE = fraction of eaten feed (-)
 1000 = correction factor to convert from mg to g
 $k_{assimilation}$ = drug assimilation rate constant in the cultured species ($\frac{\mu\text{g} \cdot \text{kg cultured species}^{-1}}{\mu\text{g} \cdot \text{kg food}^{-1}} \cdot 1/\text{d}$)
 SFR = daily specific feeding rate ($\text{kg food}/\text{kg cultured species}$)
 w = organism weight (kg)
 w_{SFR} = organism's weight at which SFR was determined (kg)
 κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)

The drug mass biochemical degradation process in the pond sediment at reference temperature is considered to follow a first order kinetics and is calculated by:

$$M_{degradation} = A \cdot h_{pond-sediment} \cdot \rho \cdot k_s(T) \cdot PSC \quad (\text{Eq. 53})$$

with,

$M_{degradation}$ = drug mass loss rate due to degradation processes in the sediment (g/d)
 A = area of the pond (m^2)
 $h_{pond-sediment}$ = depth of the top sediment layer in the aquaculture pond (m)
 ρ = sediment bulk density (kg/L)
 $k_s(T)$ = first-order degradation rate coefficient of the substance in sediment at ambient temperature (1/d)
 PSC = predicted pond sediment concentration (mg/kg)

The drug mass sorption/desorption rate from the pond sediment is considered to follow a first-order kinetics process and is calculated by:

$$M_{adsorption/desorption} = A \cdot h_{pond-sediment} \cdot \rho \cdot k_{desorption} \cdot (k_d \cdot PWC_{diss} - PSC) \quad (\text{Eq. 54})$$

with,

$M_{adsorption/desorption}$ = drug mass addition/loss rate due to sorption/desorption to sediment (g/d)
 A = area of the pond (m²)
 $h_{pond-sediment}$ = depth of the top sediment layer in the aquaculture pond (m)
 ρ = sediment bulk density (kg/L)
 $k_{desorption}$ = first-order desorption rate coefficient (1/d)
 k_d = sediment/water partitioning coefficient of the substance (L/kg)
 PWC_{diss} = predicted dissolved pond water concentration (mg/L)
 PSC = predicted pond sediment concentration (mg/kg)

Finally, combining the equations described above (Eq. 51-54) for the processes considered in the pond sediment layer, the governing equation for the drug mass balance in the pond sediment reads:

$$\begin{aligned}
 A \cdot \left(\frac{\theta_{sat}}{k_d} + \rho \right) \cdot h_{pond-sediment} \cdot \frac{\partial PSC}{\partial t} = & \left(A \cdot PERC \cdot (k_d \cdot PWC_{diss} - PSC) \right) + \left\{ (k_{egestion} \cdot PCC \cdot 10^{-6} \cdot \right. \\
 M_{CS}) + & \left. \left[\frac{DA \cdot D \cdot FE \cdot M_{CS}}{1000} \cdot \left(1 - k_{assimilation} \cdot \frac{1}{SFR \cdot \left(\frac{w}{w_{SFR}} \right)^{-\kappa}} \right) \right] \right\} - \left(A \cdot h_{pond-sediment} \cdot \rho \cdot k_s(T) \cdot PSC \right) + \\
 & \left(A \cdot h_{pond-sediment} \cdot \rho \cdot k_{desorption} \cdot (k_d \cdot PWC_{diss} - PSC) \right)
 \end{aligned} \tag{Eq. 55}$$

with,

A = area of the pond (m²)
 θ_{sat} = saturated water content of the pond sediment (v/v)
 k_d = sediment/water partitioning coefficient (L/kg)
 ρ = sediment bulk density (kg/L)
 $h_{pond-sediment}$ = depth of the top sediment layer in the aquaculture pond (m)
 PSC = predicted pond sediment concentration (mg/kg)
 $PERC$ = average daily water percolation rate (m/d)
 PWC_{diss} = predicted dissolved pond water concentration (mg/L)
 $k_{egestion}$ = drug egestion rate constant (1/d)
 PCC = predicted cultured species concentration (µg/kg)
 10^6 = correction factor to convert from µg/kg to g/kg
 M_{CS} = cultured species mass (kg)
 DA = drug administration method (DA=0 for bath treatments; DA=1 for drugs mixed with feed)
 D = individual drug dose applied (mg/L for drugs applied in bath treatments or mg/kg cultured species for drugs applied mixed with feed)
 FE = fraction of eaten feed (-)
 1000 = correction factor to convert from mg to g
 $k_{assimilation}$ = drug assimilation rate constant in the cultured species $\left(\frac{\mu\text{g} \cdot \text{kg cultured species}^{-1}}{\mu\text{g} \cdot \text{kg food}^{-1}} \cdot 1/d \right)$
 SFR = daily specific feeding rate (kg food/kg cultured species)
 w = organism weight (kg)
 w_{SFR} = organism's weight at which SFR was determined (kg)
 κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)
 $k_s(T)$ = first-order degradation rate coefficient of the substance in sediment at ambient temperature (1/d)
 $k_{desorption}$ = first-order desorption rate coefficient (1/d)

The saturated water content of the pond sediment (θ_{sat}) is considered to be the same as the fraction of the volume of voids over the total volume in the sediment (porosity), assuming water-saturated sediments in the aquaculture pond.

2.3.3 Calculation of concentrations dynamics in the cultured species

The drug concentration in the cultured species is calculated by following a first-order kinetics approach and considering two drug addition processes, drug absorption from water (absorption) and assimilation from food (assimilation), and three elimination processes, physicochemical transport with water (excretion), egestion food (egestion), and metabolic transformation (transformation). Assuming that the uptake and elimination from each of these processes is independent and additive, the governing equation for the mass balance in the cultured species reads:

$$\frac{\partial M_{\text{cultured species}}}{\partial t} = +M_{\text{absorption}} + M_{\text{assimilation}} - M_{\text{excretion}} - M_{\text{egestion}} - M_{\text{transformation}} \quad (\text{Eq. 56})$$

with,

- $M_{\text{cultured species}}$ = drug mass in the cultured species (g)
- $M_{\text{absorption}}$ = drug mass absorption rate from water by the cultured species (g/d)
- $M_{\text{assimilation}}$ = drug mass assimilation rate from food by the cultured species (g/d)
- $M_{\text{excretion}}$ = drug mass excretion rate in the cultured species (g/d)
- M_{egestion} = drug mass egestion rate in the cultured species (g/d)
- $M_{\text{transformation}}$ = drug mass transformation rate in the cultured species (g/d)

The drug mass absorption rate from water in the cultured species is calculated by:

$$M_{\text{absorption}} = k_{\text{absorption}} \cdot PWC_{\text{diss}} \cdot 10^{-3} \cdot M_{\text{CS}} \quad (\text{Eq. 57})$$

with,

- $M_{\text{absorption}}$ = drug mass absorption rate from water by the cultured species (g/d)
- $k_{\text{absorption}}$ = drug absorption rate constant in the cultured species (L/kg · d)
- PWC_{diss} = predicted dissolved pond water concentration (mg/L)
- 10^{-3} = correction factor to convert from mg/L to g/L
- M_{CS} = cultured species mass (kg)

The drug mass assimilation rate from food in the cultured species is calculated by:

$$M_{\text{assimilation}} = k_{\text{assimilation}} \cdot \frac{DA \cdot D \cdot FE}{1000 \cdot SFR \cdot \left(\frac{w}{w_{SFR}}\right)^{-\kappa}} \cdot M_{\text{CS}} \quad (\text{Eq. 58})$$

with,

- $M_{\text{assimilation}}$ = drug mass assimilation rate from food by the cultured species (g/d)
- $k_{\text{assimilation}}$ = drug assimilation rate constant in the cultured species ($\frac{\mu\text{g} \cdot \text{kg cultured species}^{-1}}{\mu\text{g} \cdot \text{kg food}^{-1}} \cdot 1/d$)
- DA = drug administration method (DA=0 for bath treatments; DA=1 for drugs mixed with feed)
- D = individual drug dose applied (mg/L for drugs applied in bath treatments or mg/kg cultured species for drugs applied mixed with feed)
- FE = fraction of eaten feed (-)
- 1000 = correction factor to convert from mg to g
- SFR = daily specific feeding rate (kg food/kg cultured species)
- w = organism weight (kg)
- w_{SFR} = organism's weight at which SFR_{ref} was determined (kg)
- κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)
- M_{CS} = cultured species mass (kg)

The rate of drug mass elimination from the cultured species by physicochemical transport with water is calculated according to:

$$M_{excretion} = k_{excretion} \cdot PCC \cdot 10^{-6} \cdot M_{CS} \quad (\text{Eq. 59})$$

with,

$M_{excretion}$ = drug mass addition rate due to excretion in the cultured species (g/d)

$k_{excretion}$ = drug excretion rate constant (1/d)

PCC = predicted cultured species concentration ($\mu\text{g}/\text{kg}$)

10^{-6} = correction factor to convert from $\mu\text{g}/\text{kg}$ to g/kg

M_{CS} = cultured species mass (kg)

The rate of drug mass eliminated from the cultured species by faeces is calculated by:

$$M_{egestion} = k_{egestion} \cdot PCC \cdot 10^{-6} \cdot M_{CS} \quad (\text{Eq. 60})$$

with,

$M_{egestion}$ = drug mass addition rate due to egestion by the cultured species (g/d)

$k_{egestion}$ = drug egestion rate constant (1/d)

PCC = predicted cultured species concentration ($\mu\text{g}/\text{kg}$)

10^{-6} = correction factor to convert from $\mu\text{g}/\text{kg}$ to g/kg

M_{CS} = cultured species mass (kg)

The rate of drug mass metabolized in the cultured species is calculated by:

$$M_{transformation} = k_{transformation} \cdot PCC \cdot 10^{-6} \cdot M_{CS} \quad (\text{Eq. 61})$$

with,

$M_{transformation}$ = drug mass transformation rate in the cultured species (g/d)

$k_{transformation}$ = drug biotransformation rate constant (1/d)

PCC = predicted cultured species concentration ($\mu\text{g}/\text{kg}$)

10^{-6} = correction factor to convert from $\mu\text{g}/\text{kg}$ to g/kg

M_{CS} = cultured species mass (kg)

Finally, combining the equations described above (Eq. 57-61) for the uptake and elimination processes considered in the cultured species, the governing equation for the drug mass balance in the cultured species reads:

$$10^{-6} \cdot \frac{\partial(M_{CS} \cdot PCC)}{\partial t} = \left(10^{-6} \cdot \frac{\partial M_{CS}}{\partial t} \cdot PCC \right) + \left(10^{-6} \cdot \frac{\partial PCC}{\partial t} \cdot M_{CS} \right) + \left(10^{-6} \cdot \frac{\partial M_{CS}}{\partial t} \cdot \frac{\partial PCC}{\partial t} \right) = \left(k_{absorption} \cdot PWC_{diss} \cdot 10^{-3} \cdot M_{CS} \right) + \left(k_{assimilation} \cdot \frac{DA \cdot D \cdot FE}{1000 \cdot SFR \cdot \left(\frac{w}{wSFR} \right)^{-\kappa}} \cdot M_{CS} \right) - \left((k_{excretion} + k_{egestion} + k_{transformation}) \cdot PCC \cdot 10^{-6} \cdot M_{CS} \right) \quad (\text{Eq. 62})$$

with,

M_{CS} = cultured species mass (kg)

10^{-6} = correction factor to convert from $\mu\text{g}/\text{kg}$ to g/kg

PCC = predicted cultured species concentration ($\mu\text{g}/\text{kg}$)

$k_{absorption}$ = drug absorption rate constant in the cultured species ($\text{L}/\text{kg} \cdot \text{d}$)

PWC_{diss} = predicted dissolved pond water concentration (mg/L)

10^3 = correction factor to convert from mg/L to g/L

$k_{assimilation}$ = drug assimilation rate constant in the cultured species ($\frac{\mu\text{g} \cdot \text{kg cultured species}^{-1}}{\mu\text{g} \cdot \text{kg food}^{-1}} \cdot 1/d$)

DA = drug administration method ($DA=0$ for bath treatments; $DA=1$ for drugs mixed with feed)

D = individual drug dose applied (mg/L for drugs applied in bath treatments or mg/kg cultured species for drugs applied mixed with feed)

FE = fraction of eaten feed (-)

1000 = correction factor to convert from mg to g

SFR = daily specific feeding rate (kg food/kg cultured species)

w = organism weight (kg)

w_{SFR} = organism's weight at which SFR was determined (kg)

κ = rate exponent (-) (constant parameter = 0.25; Hendriks et al., 2001)

$k_{excretion}$ = drug excretion rate constant (1/d)

$k_{egestion}$ = drug egestion rate constant (1/d)

$k_{transformation}$ = drug biotransformation rate constant (1/d)

2.4 Calculation of the peak PWC_{total}

To assess the potential risks of acute drug exposure for the cultured species, the peak PWC_{total} , the PWC_{diss} and the PWC_{ss} are calculated as the highest value of the time series calculated for the whole simulation period (Figure 2).

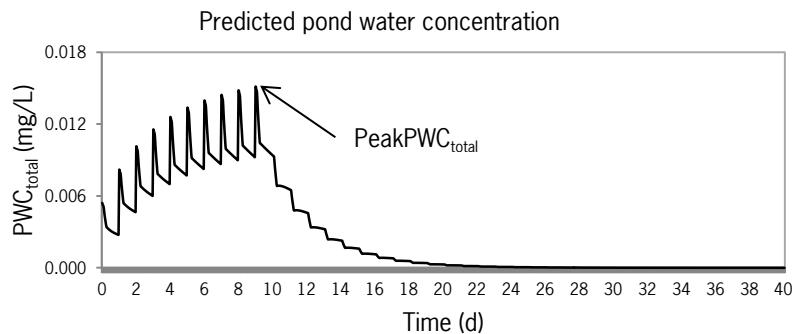


Figure 2

Example of Total Predicted pond Water Concentration dynamics (PWC_{total}) and peak Total Predicted pond Water Concentration ($PeakPWC_{total}$) of the drug in the pond water. Example data showed for the first 40 days of the simulation period.

2.5 Calculation of $PCC_{harvest}$

In order to calculate the potential risks for consumers and trade, the predicted concentration in the cultured species on the planned harvest day is calculated ($PCC_{harvest}$) (see Figure 3). This could help farmers to take decisions on what is the most appropriate moment to harvest the cultured species in order to do not exceed given drug threshold concentrations in the cultured species. Alternatively, withdrawal periods have been established for each veterinary medicinal product concerning the pharmaceutical form, the administration route and the duration of the treatment. The withdrawal period of the drug in the cultured species can be defined as the minimum waiting time required before the concentration of the applied drug in the cultured organisms has been reduced to levels below the maximum permitted limits and therefore the animals can be

slaughtered. Each withdrawal day is a full 24 hours, starting from the last time the animal received the drug treatment. Withdrawal periods, however, can vary depending on the species, aquaculture management practices and environmental conditions. Therefore, the estimation of the $PCC_{harvest}$ is more realistic than solely relying on the use of recommended withdrawal periods, and could help to quantify potential risks for consumers and/or trade based on specific aquaculture practices (e.g., limited water exchange), specific environmental conditions (e.g., different temperature conditions to the experimental set-up in which the recommended withdrawal period has been calculated) and when cases of mismanagement occur (e.g., not respecting the recommended withdrawal period).

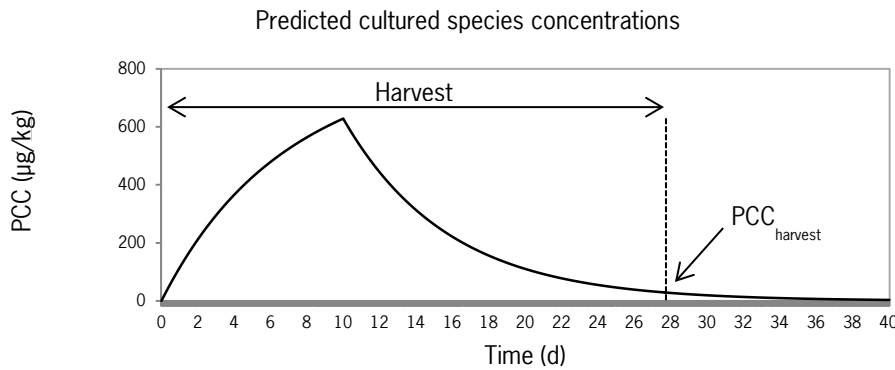


Figure 3

Example of Predicted Cultured species Concentration dynamics (PCC), planned harvest day after the start of the simulation period (Harvest), and Predicted Cultured species Concentration at harvest ($PCC_{harvest}$). Example data showed for the first 40 days of the simulation period.

2.6 Calculation of drug concentrations in the watercourse

2.6.1 Calculation of PECs

Predicted Environmental Concentrations (PECs) of the drug in the watercourse are calculated in the effluent discharge point (mixing zone). The momentary PEC in the effluent discharge point of the watercourse produced during the effluent discharge depends on the predicted total pond water concentration at the moment of the effluent discharge and the dilution of the effluent discharge in the watercourse. The model calculates the predicted total (water) environmental concentration (PEC_{total} ; sum of the dissolved fraction of the drug and the fraction sorbed to suspended solids), the predicted environmental concentration of the drug dissolved in water (PEC_{diss}) and the predicted environmental concentration of the drug sorbed to suspended solids (PEC_{ss}). The calculation of these three concentrations are based on the total drug concentration in the pond water layer, the dissolved concentration in the pond water layer, and the concentration of the drug sorbed to suspended solids in the pond water layer, respectively. Environmental concentrations are calculated by:

$$PEC_{total} = \frac{PWC_{total} \cdot Q_{effluent}}{Q_{watercourse} + Q_{effluent}} \quad (\text{Eq. 63})$$

$$PEC_{diss} = \frac{PWC_{diss} \cdot Q_{effluent}}{Q_{watercourse} + Q_{effluent}} \quad (\text{Eq. 64})$$

$$PEC_{ss} = \frac{PWC_{ss} \cdot Q_{effluent}}{Q_{watercourse} + Q_{effluent}} \quad (\text{Eq. 65})$$

with,

PEC_{total} = predicted total environmental concentration (mg/L)

PWC_{total} = predicted total drug concentration in the pond's water (mg/L)

$Q_{effluent}$ = effluent flow (L/s)

$Q_{watercourse}$ = water flow in the watercourse (L/s)

PEC_{diss} = predicted dissolved environmental concentration (mg/L)

PWC_{diss} = predicted dissolved pond water concentration (mg/L)

PEC_{ss} = predicted environmental concentration of the drug sorbed to suspended solids (mg/L)

PWC_{ss} = predicted concentration of the drug in the pond water sorbed to suspended solids (mg/L)

The effluent flow is calculated by taking into account the volume of water discharged in the specific day the effluent discharge takes place and the average duration of the effluent discharge according to:

$$Q_{effluent} = \frac{DRAIN \cdot A \cdot 1000}{t_{effluent} \cdot 3600} \quad (\text{Eq. 66})$$

with,

$Q_{effluent}$ = effluent flow (L/s)

$DRAIN$ = average daily water drainage (m)

A = area of the pond (m²)

1000 = correction factor to convert from m³ to L

$t_{effluent}$ = duration of the effluent discharge (h)

3600 = correction factor to convert from hours to seconds

The duration of the effluent discharge is assumed to be the same for all the water discharges over the simulation period.

The water flow in the watercourse is calculated by multiplying the cross section of the watercourse by the measured water flow velocity in the watercourse:

$$Q_{stream} = A_{watercourse} \cdot v_{watercourse} \cdot 1000 \quad (\text{Eq. 67})$$

with,

Q_{stream} = baseline stream flow (L/s)

$A_{watercourse}$ = cross section of the water layer in the watercourse (m²)

$v_{watercourse}$ = flow velocity in the watercourse (m/s)

1000 = correction factor to convert from m³/s to L/s

The cross section of the watercourse is calculated by:

$$A_{watercourse} = h_{watercourse} \cdot b + h_{watercourse}^2 \cdot s \quad (\text{Eq. 68})$$

(Peeters et al. 2008) with,

$A_{watercourse}$ = cross section of the water layer in the watercourse (m²)

$h_{watercourse}$ = depth of water layer in the watercourse (m)

b = bottom width of water body in the watercourse (m)

s = side slope, horizontal/vertical, in the watercourse (-)

Once the effluent discharge stops, the drug residues in the effluent discharge point are assumed to dissipate immediately since they are transported down-stream with the water flow.

2.6.2 Calculation of the peak PEC

In order to assess the risks of acute drug exposure for aquatic organisms inhabiting the watercourses receiving effluent discharges, the peak PEC_{total} , the peak PEC_{diss} , and the peak PEC_{ss} are calculated. The peak PECs are calculated as the highest momentary predicted exposure concentration produced in the watercourse during the simulation period (Figure. 4).

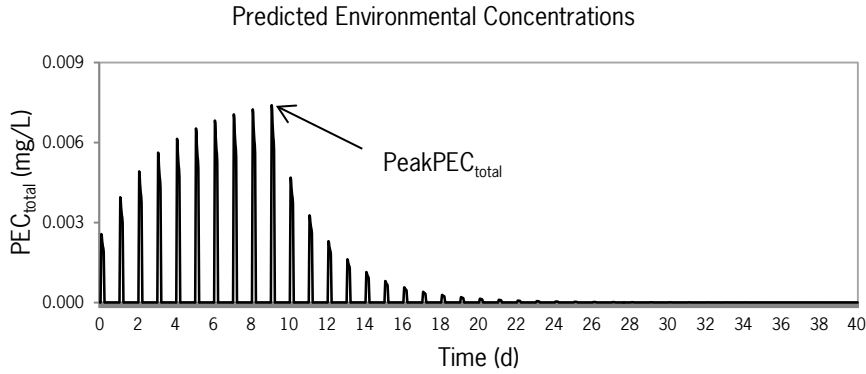


Figure 4
Example of Total Predicted Environmental Concentration dynamics (PEC_{total}) and Total peak Predicted Environmental Concentration ($PeakPEC_{total}$). Example data showed for the first 40 days of the simulation period with a duration of the effluent discharge of 5h.

2.6.3 Calculation of predicted environmental TWA concentrations

In order to assess chronic drug exposure concentrations for aquatic organisms in the watercourse, Time Weighted Average (TWA) concentrations of the Predicted Environmental Concentrations (PEC_{total} , PEC_{diss} , PEC_{ss}) are calculated for a time period of 3, 21 and 28 days. The TWA concentration of the drug in the watercourse is calculated in each simulation time step considering the three different time periods by Eq. 69. Finally, the maximum of the calculated TWAs for each length period is conservatively chosen as the TWA for the simulation period.

$$TWA_i = \frac{\sum_i^k PEC_j}{t_{TWA} \cdot 1440} \quad (\text{Eq. 69})$$

with,

i = time step, $i \leq t + 1 - (t_{TWA} \cdot 1440)$

t = simulation period (d) $\cdot 1440$

$k = i + (t_{TWA} \cdot 1440) - 1$, $k \leq t$

$j \in [i, k]$

$TWA_{t_{TWA}}$ = Time Weighted Average concentration for the period with length t_{TWA} (mg/L)

PEC = predicted environmental concentration produced by the effluent discharge in the i time step (mg/L)

t_{TWA} = length of period for TWA (TWA_3 : $t_{twa}=3d$; TWA_{21} : $t_{twa}=21d$; TWA_{28} : $t_{twa}=28d$)

1440 = number of minutes in one day

2.7 Numerical solution

The differential equations 24, 29, 45, 49 and 55 are simultaneously solved in Office EXCEL 2010 (through a VBA code) for $h_{\text{pond-water}}$, M_{CS} , $\text{PWC}_{\text{total}}$, PWC_{diss} , PWC_{SS} , PSC and PCC in time steps of one minute during the whole simulation period. Subsequently, the model calculates the peak $\text{PWC}_{\text{total}}$, the $\text{PCC}_{\text{harvest}}$, the peak $\text{PEC}_{\text{total}}$, the peak PEC_{diss} , the peak PEC_{SS} , and the TWA concentrations in the environment. The following assumptions are applied during the numerical solution of the equations: i) there is a maximum of one drug application and one effluent discharge per day, and ii) the water exchange event takes place 2h after the drug is applied in the aquaculture pond.

3 Aquatic effect assessment

3.1 Effect assessment for the cultured species

The safety of the drug treatment for the cultured species is assessed by calculating a short-term Predicted No Effect Concentration (PNEC) for the cultured species by:

$$PNEC_{cultured-species} = \frac{EC50_{cultured-species}}{AF_{cultured-species}} \quad (\text{Eq. 70})$$

with,

$PNEC_{cultured-species}$ = predicted no effect concentration for the cultured species (mg/L)

$AF_{cultured-species}$ = assessment factor for short-term effect assessment on the cultured species (default value = 10)

$EC50_{cultured-species}$ = concentration that affects 50% of the test organisms, cultured species (mortality or growth inhibition in mg/L)

The assessment factor for short-term effect assessment on the cultured species accounts for the extrapolation from 50% effect to no effect in the cultured species population.

3.2 Effect assessment for aquatic ecosystems

Acute and chronic PNECs are calculated for three different taxonomic groups of aquatic organisms (i.e., algae, invertebrates and fish) with toxicity data for standard test species and an assessment factor. According to the international guidelines on the environmental impact assessment for veterinary products published by the VICH (International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products), at least one fish, one aquatic invertebrate (preferably *Daphnia* for freshwater ecosystems) and one algal species need to be tested for the registration and evaluation of veterinary medicines that are expected to result in environmental concentrations higher than 1 µg/L and for all kind of compounds used to kill parasites in the cultured species (VICH, 2000 and 2004). A number of standard test procedures for the calculation of acute and chronic toxicity data of veterinary medicinal products for freshwater and saltwater species are proposed in VICH (2004).

3.2.1 Effect assessment: acute exposure

Acute PNECs for algae, invertebrates and fish are calculated according to the following equations:

$$PNEC_{acute-algae} = \frac{EC50_{acute-algae}}{AF_{acute-algae}} \quad (\text{Eq. 71})$$

$$PNEC_{acute-invertebrates} = \frac{EC50_{acute-invertebrates}}{AF_{acute-invertebrates}} \quad (\text{Eq. 72})$$

$$PNEC_{acute-fish} = \frac{EC50_{acute-fish}}{AF_{acute-fish}} \quad (\text{Eq. 73})$$

with,

$PNEC_{acute-algae}$ = acute predicted no effect concentration for algae (mg/L)

$PNEC_{acute-invertebrates}$ = acute predicted no effect concentration for invertebrates (mg/L)

$PNEC_{acute-fish}$ = acute predicted no effect concentration for fish (mg/L)

$AF_{acute-algae}$ = assessment factor for acute effect assessment of algae (default value = 100)

$AF_{acute-invertebrates}$ = assessment factor for acute effect assessment of invertebrates (default value = 100)

$AF_{acute-fish}$ = assessment factor for acute effect assessment of fish (default value = 100)

$EC50_{acute-algae}$ = concentration that affects 50% of the test organisms, algae (growth inhibition in mg/L)

$EC50_{acute-invertebrates}$ = concentration that affects 50% of the test organisms, Daphnia (immobilization in mg/L)

$LC50_{acute-fish}$ = concentration that kills 50% of the test organisms, fish (mg/L)

The assessment factors given by model as default values correspond with those proposed by the VICH for the environmental impact assessment of veterinary medicinal products used in aquaculture (VICH 2004).

3.2.2 Effect assessment: chronic exposure

Chronic PNECs for algae, invertebrates and fish are calculated according to the following equations:

$$PNEC_{chronic-algae} = \frac{NOEC_{chronic-algae}}{AF_{chronic-algae}} \quad (\text{Eq. 74})$$

$$PNEC_{chronic-invertebrates} = \frac{NOEC_{chronic-invertebrates}}{AF_{chronic-invertebrates}} \quad (\text{Eq. 75})$$

$$PNEC_{chronic-fish} = \frac{NOEC_{chronic-fish}}{AF_{chronic-fish}} \quad (\text{Eq. 76})$$

with,

$PNEC_{chronic-algae}$ = chronic predicted no effect concentration for algae (mg/L)

$PNEC_{chronic-invertebrates}$ = chronic predicted no effect concentration for invertebrates (mg/L)

$PNEC_{chronic-fish}$ = chronic predicted no effect concentration for fish (mg/L)

$AF_{chronic-algae}$ = assessment factor for chronic effect assessment of algae (default value = 10)

$AF_{chronic-invertebrates}$ = assessment factor for chronic effect assessment of invertebrates (default value = 10)

$AF_{chronic-fish}$ = assessment factor for chronic effect assessment of fish (default value = 10)

$NOEC_{chronic-algae}$ = chronic no observed effect concentration for algae (growth inhibition in mg/L)

$NOEC_{chronic-invertebrates}$ = chronic no observed effect concentration for invertebrates, Daphnia magna (reproduction or chronic toxicity test, mg/L)

$NOEC_{chronic-fish}$ = chronic no observed effect concentration for fish (early-life stage test or chronic toxicity test, mg/L)

The $NOEC_{chronic-algae}$ can be derived using the same study in which $EC50_{acute-algae}$ was calculated (VICH, 2004). The assessment factors correspond with those proposed by the VICH for the environmental impact assessment of veterinary medicinal products used in aquaculture (VICH, 2004).

4 Risk assessment

Risks for the cultured species, for aquatic ecosystems and for consumers and trade are assessed by following a Risk Quotient (RQ) approach according to the equations described below.

4.1 Risk assessment for the cultured species

The potential risk of the chemical treatment for the cultured species is assessed by means of a short-term RQ for the cultured species calculated by:

$$RQ_{\text{cultured-species}} = \frac{\text{Peak } PWC_{\text{total}}}{PNEC_{\text{cultured-species}}} \quad (\text{Eq. 77})$$

with,

$RQ_{\text{cultured-species}}$ = risk quotient for the cultured species (-)

$\text{Peak } PWC_{\text{total}}$ = highest momentary predicted total pond water concentration during the simulation period (mg/L)

$PNEC_{\text{cultured-species}}$ = predicted no effect concentration for the cultured species (mg/L)

lf:	$RQ < 1$	No Exceedance	(indicated by green color)
	$1 \leq RQ \leq 10$	Exceedance	(indicated by yellow color)
	$RQ > 10$	Large Exceedance	(indicated by red color)

The model calculates the $RQ_{\text{cultured-species}}$ based on the $\text{Peak } PWC_{\text{total}}$ by default. However, note that this can lead to an overestimation of the risks for aquaculture species that only take up the freely dissolved concentration and to an underestimation of the risks for those species that dwell on the sediment surface. Since the model also provides the freely dissolved concentrations of the drug in the pond water and the concentrations of the drug in the top sediment layer, the user must decide which is the most relevant concentration for assessing the risks for the cultured species on a case-by-case basis. The experimental set-up and the major exposure routes in the toxicity study used to calculate the PNEC for the cultured species must be taken into account to decide the most relevant exposure concentration for the cultured species.

4.2 Risk assessment for aquatic ecosystems

4.2.1 Acute risk assessment for aquatic ecosystems

Acute risks for algae, invertebrates and fish in aquatic ecosystems receiving aquaculture effluents are expressed by means of acute RQs calculated by:

$$RQ_{\text{acute-algae}} = \frac{\text{Peak } PEC_{\text{total}}}{PNEC_{\text{acute-algae}}} \quad (\text{Eq. 78})$$

$$RQ_{\text{acute-invertebrates}} = \frac{\text{Peak } PEC_{\text{total}}}{PNEC_{\text{acute-invertebrates}}} \quad (\text{Eq. 79})$$

$$RQ_{\text{acute-fish}} = \frac{\text{Peak } PEC_{\text{total}}}{PNEC_{\text{acute-fish}}} \quad (\text{Eq. 80})$$

with,

$RQ_{acute-algae}$ = acute risk quotient for algae (-)

$RQ_{acute-invertebrates}$ = acute risk quotient for invertebrates (-)

$RQ_{acute-fish}$ = acute risk quotient for fish (-)

$Peak\ PEC_{total}$ = highest momentary total predicted environmental concentration (mg/L)

$PNEC_{acute-algae}$ = acute predicted no effect concentration for algae (mg/L)

$PNEC_{acute-invertebrates}$ = acute predicted no effect concentration for invertebrates (mg/L)

$PNEC_{acute-fish}$ = acute predicted no effect concentration for fish (mg/L)

If:	$RQ < 1$	No Exceedance	(indicated by green color)
	$1 \leq RQ \leq 10$	Exceedance	(indicated by yellow color)
	$RQ > 10$	Large Exceedance	(indicated by red color)

The model calculates risks for aquatic organisms in the watercourse based on the $PeakPEC_{total}$ by default. Please note that for some species of algae and floating macrophytes the freely dissolved concentration should be considered as the most ecologically relevant exposure concentration rather than the total drug concentration, and the use of the total drug concentration could lead to an overestimation of the risk. For most of the zooplankton species the total concentration must be chosen given their capability to filter and feed on suspended particles, whereas for benthic invertebrates the total concentration could lead to an underestimation of the risk since they can be exposed via water and via contaminated sediment. For pelagic fish, for example, the total concentration can be (conservatively) assumed whereas for benthic fish the total concentration could lead to an underestimation of the risk. The choice of the relevant exposure concentration in the risk assessment for each species or group of species must be carefully done in a case-by-case basis, taking into account the main exposure routes of the species under study and the experimental set-up of the toxicity studies used to calculate the PNEC. Most of the single-species laboratory toxicity studies are performed with water containing an insignificant concentration of suspended solids, and thus the absorption via water (i.e., dissolved chemical fraction) could be considered as the main route of exposure in such experiments.

4.2.2 Chronic risk assessment for aquatic ecosystems

Chronic risks for algae, invertebrates and fish in aquatic ecosystems receiving aquaculture effluents are expressed by means of chronic RQs calculated by:

$$RQ_{chronic-algae} = \frac{TWA_3\ total}{PNEC_{chronic-algae}} \quad (\text{Eq. 81})$$

$$RQ_{chronic-invertebrates} = \frac{TWA_{21}\ total}{PNEC_{chronic-invertebrates}} \quad (\text{Eq. 82})$$

$$RQ_{chronic-fish} = \frac{TWA_{28}\ total}{PNEC_{chronic-fish}} \quad (\text{Eq. 83})$$

with,

$RQ_{chronic-algae}$ = acute risk quotient for algae (-)

$RQ_{chronic-invertebrates}$ = acute risk quotient for invertebrates (-)

$RQ_{chronic-fish}$ = acute risk quotient for fish (-)

$TWA_3\ total$ = Total Time Weighted Average concentration for algae (default period of length = 3 days, mg/L)

$TWA_{21}\ total$ = Total Time Weighted Average concentration for invertebrates (default period of length = 21 days, mg/L)

$TWA_{28}\ total$ = Total Time Weighted Average concentration for fish (default period of length = 28 days, mg/L)

$PNEC_{\text{chronic-algae}}$ = chronic predicted no effect concentration for algae (mg/L)

$PNEC_{\text{chronic-invertebrates}}$ = chronic predicted no effect concentration for invertebrates (mg/L)

$PNEC_{\text{chronic-fish}}$ = chronic predicted no effect concentration for fish (mg/L)

If:	$RQ < 1$	No Exceedance	(indicated by green color)
	$1 \leq RQ \leq 10$	Exceedance	(indicated by yellow color)
	$RQ > 10$	Large Exceedance	(indicated by red color)

The model calculates risks for aquatic organisms in the watercourse based on the total TWA concentrations by default. Please consider the arguments discussed in Section 4.2.1 for the choice of the most relevant exposure concentration for each species or group of aquatic organisms.

4.3 Risk assessment for consumers

Long-term risks for consumers are estimated by comparing the Estimated Daily Intake (EDI) of the chemical in humans with Acceptable Daily Intake (ADI) values. The EDI is estimated based on the concentration of the drug in the cultured species in the moment of harvest, the daily consumption of the cultured species and the consumer's body weight:

$$EDI = \frac{PCC_{\text{harvest}} \cdot Cons}{1000 \cdot bw} \quad (\text{Eq. 84})$$

with,

EDI = estimated daily intake of the drug (mg/kg · d)

PCC_{harvest} = predicted drug concentration in the cultured species at harvest (µg/kg)

$Cons$ = daily consumption of the cultured species (kg/d)

1000 = correction factor to convert from µg/kg to mg/kg

bw = consumer's body weight (default value = 60kg for adults)

Different local diets can be used for the estimation of the daily consumption of the cultured species. For example, the World Health Organization (WHO) average daily intake estimation for the Far East is 32 g for fish and seafood (WHO, 2003).

The ADI is an estimate of the amount of a substance (expressed on a body weight basis) which can be ingested daily over a lifetime without appreciable health risk to the consumer. The ADI is typically set on the basis of toxicological, pharmacological or microbiological studies with mammals. ADIs are frequently calculated based on the No Observed Adverse Effect Level (NOAEL) value for mammals and an extrapolation factor accounting for intraspecies variability and interspecies extrapolation. ADI values are frequently available in the literature, however when these are not available they are calculated by the model according to Eq. 85.

$$ADI = \frac{NOAEL_{\text{mammals}}}{EF_{\text{mammals}}} \quad (\text{Eq. 85})$$

with,

ADI = acceptable daily intake for the drug (mg/kg · d)

$NOAEL_{\text{mammals}}$ = no observed adverse effect level for mammals (mg/kg · d)

EF_{mammals} = extrapolation factor to account for interspecies and intraspecies extrapolation (default value = 100)

An extrapolation factor of 100 is used by the model as default value. This extrapolation factor is typically used to derive ADIs for humans from NOAELs calculated for mammals (e.g. rats) (Benford, 2000). However,

according to the relevance and the quality of the toxicological/pharmacological data available, safety factors can range from 10 to 1000 (Benford, 2000).

The dietary risk for consumers is expressed by a RQ as follows:

$$RQ_{consumers} = \frac{EDI}{ADI} \quad (\text{Eq. 86})$$

with,

$RQ_{consumers}$ = risk quotient for consumers (-)

EDI = estimated daily intake of the drug (mg/kg · d)

ADI = acceptable daily intake for the drug (mg/kg · d)

If:	$RQ < 1$	No Exceedance	(indicated by green color)
	$1 \leq RQ \leq 10$	Exceedance	(indicated by yellow color)
	$RQ > 10$	Large Exceedance	(indicated by red color)

4.4 Risk assessment for trade

National and international food safety control programs for aquaculture products have set specific Maximum Residue Limits (MRLs) for veterinary medicines and other chemicals in fish and seafood products (e.g. EU, 2010). Shipments of products containing chemical residue levels exceeding these MRLs will be rejected and, hence, the compliance with these MRLs is of major importance for the trade of the aquaculture produce. Risks for the trade of the aquaculture produce based on MRLs are calculated by:

$$RQ_{trade} = \frac{PCC_{harvest}}{MRL} \quad (\text{Eq. 87})$$

with,

RQ_{trade} = risk quotient for consumers and trade (-)

$PCC_{harvest}$ = predicted drug concentration in the cultured species at harvest (µg/kg)

MRL = maximum residue limit in the cultured species (µg/kg)

If:	$RQ < 1$	No Exceedance	(indicated by green color)
	$1 \leq RQ \leq 10$	Exceedance	(indicated by yellow color)
	$RQ > 10$	Large Exceedance	(indicated by red color)

5 User's manual

5.1 Getting started

5.1.1 Installation

The ERA-AQUA Decision Support System v2.0 can be freely downloaded from: www.era-aqua.wur.nl. The ERA-AQUA Decision Support System has been tested under Microsoft EXCEL 2007, Microsoft EXCEL 2010 and Microsoft EXCEL 2011 for Mac. Before to download the ERA-AQUA model make sure that one of these versions is properly installed in your computer. The generation of risk assessment reports requires Microsoft Word to be installed on your computer as well. The program file does not need any additional components to be installed for its functioning and can be executed as a regular EXCEL file. Since the model calculations are implemented as Visual Basic script, the user must allow the Macros in the ERA-AQUA EXCEL file to be executed. When you have problems with this please contact your system administrator.

5.1.2 Resolution

The screen resolution recommended for an optimal use of the ERA-AQUA Decision Support System is 800x600 pixels or higher.

5.1.3 Model structure

The ERA-AQUA Decision Support System works through a Visual Basic code that performs the modeling calculations described in the present manual. The user interface is divided into six input data spreadsheets and six output data spreadsheets. Advices on how to perform a risk assessment and make use of each of the input and output spreadsheets are provided in the next section.

5.2 Perform a risk assessment

In order to perform a risk assessment, open the ERA-AQUA v2.0 EXCEL file and click on enabling macros (if requested by the program). First, the user must fill in the model input parameters.

5.2.1 Model input

When the ERA-AQUA v2.0 file is opened the 'Intro' spreadsheet will automatically appear (Figure 5). There are two options to input parameter values in the model: by loading parameter files or by manually introducing the input data. For loading parameter files, first, fill in the 'ScenarioParameters' and 'DrugParameters' excel files provided together with the model, and subsequently save and close them. These input parameter files contain default values provided by the model in bold. Then, go to the 'Intro' spreadsheet and click on the 'Load parameter file' button. Select the 'ScenarioParameters' and open it. Then, select the 'DrugParameters' file and open it. Check that the input data stored in 'ScenarioParameters' and 'DrugParameters' has been properly uploaded by revising each of the input data spreadsheets (i.e., Intro, ScenarioA, ScenarioB, WaterDrugInOut,

DrugA and Drug B). When the parameters have been successfully uploaded, the original color of the input parameter cells (i.e., orange) will turn grey. In addition, the color of the input parameter spreadsheet tag located at the bottom of your screen will turn from red (original color) to green, indicating that the input parameter values contained in the given spreadsheet are complete. Please note that most of the input parameters are subject to parameter ranges. When one of the input parameter values does not fall within the allowed range, the cell will remain orange. A message will appear by clicking on the specific cell indicating the allowed parameter value range. When this situation happens, the input parameter spreadsheet tag located at the bottom of the screen will remain red, warning the user that some input parameters still need to be introduced or changed according to the allowed ranges. When all the input parameters have been properly uploaded, all the input parameter spreadsheet tags will show a green color and the 'Run' button of the 'RiskAssessment' spreadsheet will turn green. This indicates that the model is ready to perform the risk assessment calculations. An explanation of each of the input data spreadsheets is given below together with some guidance for introducing the input data manually.

1) *Introduce the scenario and the compound's name*

Type the scenario name and compound name in the indicated cells. When doing so, the cells will turn grey and the typed scenario and compound name will be automatically displayed in the input scenario and drug parameters spreadsheets.

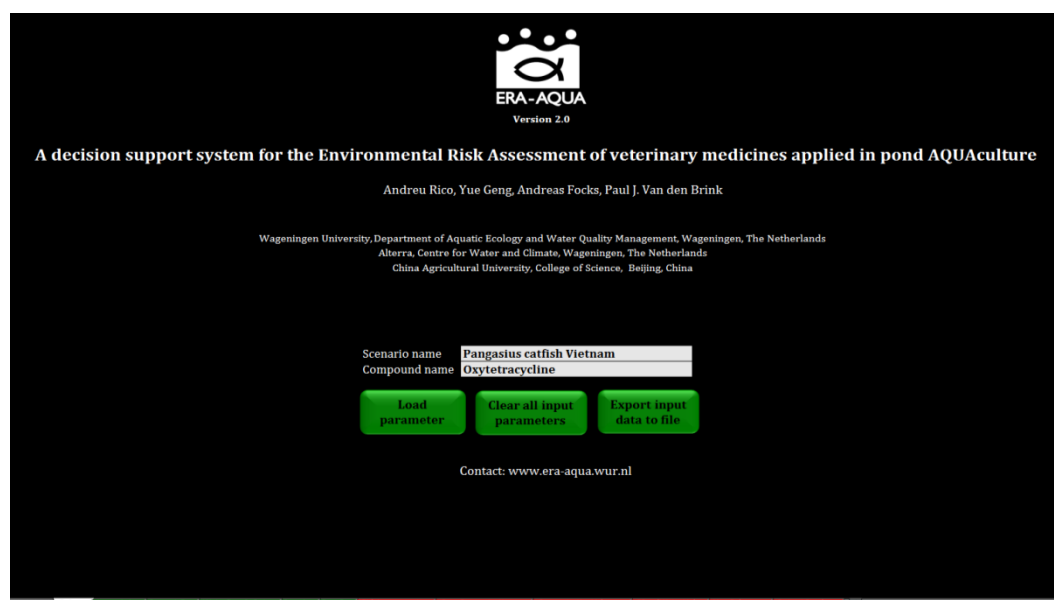


Figure 5
Intro spreadsheet of ERA-AQUA v2.0.

This spreadsheet contains three buttons. From left to right, the first button called 'Load parameter file' is used to upload input parameter files as explained above. The second and third button are only useful when data is entered manually. The second button, called 'Clear all input parameters', can be used to clear all the input parameters from the input data spreadsheets and start a new simulation by inputting new parameter values. The third button, called 'Export input data', can be used to export all the input parameter values entered manually to an excel file that can later be used as input file.

2) Scenario characteristics

Open the 'Scenario A' spreadsheet by clicking on the spreadsheet tag at the bottom of the screen. Fill in the 'Aquaculture pond' and the 'Watercourse' (drainage water body) input parameters. Recommended values for the pond sediment porosity are provided (top right corner of the spreadsheet) based on different sediment textures (Figure 6). Please keep in mind that in order to perform model calculations excluding the sediment compartment (i.e., aquaculture tanks) the parameter $h_{pond\ sediment}$ must be set to zero.

SCENARIO PARAMETERS (A) Scenario: **Pangasius catfish Vietnam**

Aquaculture pond

A	Area of the pond	6100	m ²
$h_{pond\ water}$	Initial depth of water layer in the aquaculture pond	4	m
SS	Mass concentration of suspended solids in pond water	0.000061	kg/L
$m_{om,ss}$	Mass fraction of organic matter in suspended solids	0.5	g/g
$h_{pond\ sediment}$	Depth of the top sediment layer in the aquaculture pond	0.05	m
f_{om}	Mass fraction of organic matter in sediment	0.085	(-)
ϕ	Sediment porosity ^a	0.51	v/v
ρ	Sediment bulk density	0.8	g/cm ³
T	Average ambient temperature in the modelled scenario	27.1	°C
PERC	Average daily percolation rate	0	m/d
RAIN	Average daily rainfall rate	0.0048	m/d
EVAP	Average daily evaporation rate	0.003	m/d

Watercourse

$v_{watercourse}$	Flow velocity in the watercourse	0.1	m/s
$h_{watercourse}$	Depth of water layer in the watercourse	4	m
b	Bottom width of water body in the watercourse	8	m
s	Side slope, horizontal/vertical, in the watercourse	0.3	(-)

^a Recommended values: ϕ

Sediment Texture	Porosity (v/v)
Sand	0.38
Sandy Loam	0.43
Loam	0.47
Clay Loam	0.49
Silty Clay	0.51
Clay	0.53

Figure 6

Scenario A spreadsheet of ERA-AQUA v2.0.

Open the 'Scenario B' spreadsheet and fill in the 'Cultured species', 'Feed input to the cultured species' and 'Consumer characteristics' parameters (Figure 7).

SCENARIO PARAMETERS (B) Scenario: **Pangasius catfish Vietnam**

Cultured species

w_0	Organism weight at the start of the simulation period	0.8	kg
w_{max}	Maximum organism weight	1	kg
ρ_{cs}	Cultured species density at the start of the simulation	26.88	kg/m ²
ρ_{chl}	Lipid fraction of cultured organisms	0.0255	(-)
MORT	Mortality fraction during the culture cycle	0.05	(-)
ρ_{H2O}	Partial water layer diffusion resistance to and from water	0.0068	d · kg ⁻¹
$\rho_{H2O,food}$	Partial water layer diffusion resistance to and from food	0.0002	d · kg ⁻¹
ρ_{chl}	Lipid layer permeation resistance	97	d · kg ⁻¹
γ_0	Water absorption-excretion coefficient	4200	kg ⁻¹ /d

Feed input to the cultured species

SFR	Daily specific feeding rate	0.032	(kg food/kg BW) / d
w_{SFR}	Organism's weight at which SFR was determined	0.337	kg
$\rho_{chl,food}$	Lipid fraction of food	0.05	(-)
FCR	Feed conversion ratio in the cultured species	1.69	kg food/kg BW
FE	Fraction of eaten feed	0.95	(-)

Consumer characteristics

Cons	Daily consumption of the cultured species	0.095	kg/d
bw	Consumer's body weight	60	kg

BW: body weight of the cultured organisms

Figure 7

Scenario B spreadsheet of ERA-AQUA v2.0.

3) Water exchange management and drug application

Open the 'WaterDrugInOut' spreadsheet and an empty table of days representing the simulation period will be displayed (Figure 8). The water exchange dynamics in the aquaculture pond must be programmed by the user by entering the average water irrigation and drainage (in meters of water depth per day) for each day of the simulation period. If there is not water exchange for a given day please type zero in the irrigation and drainage cells. Fill in the duration of the daily effluent discharge (in hours). For performing simulations for flow-through ponds (continuous water exchange) the user must type 24h in the duration of the effluent discharge. Select a stocking day and a duration of the simulation period (maximum 365 days). If the programmed model run assumes that the cultured species was stocked before the start of the simulation period type zero as stocking day. Next, fill in the (predicted or measured) dissolved drug concentration in the in-flow water (in mg/L) for each day of the simulation period. This function might allow the user to perform simulations connecting ponds that receive water discharges from other ponds or to perform risk assessments for non-aquaculture chemicals entering the aquaculture pond with the in-flow water. If the in-flow water is not expected to contain residues of the drug under study please type zero. Introduce the drug administration method (type zero if the drug is applied directly to water or type one if the drug is applied mixed with feed) and fill in the daily dose in the simulation period calendar. Please note that for drugs applied directly to water (bath treatments) the daily dose must be introduced in mg/L, whereas for drugs applied mixed with feed (in-feed treatments) the daily dose must be introduced in mg/kg of body weight of the cultured species. Finally, introduce the planned harvest day after the start of the simulation period.

Figure 8
WaterDrugInOut spreadsheet of ERA-AQUA v2.0.

4) Drug characteristics

Open the 'Drug A' spreadsheet and introduce the 'Physico-chemical characteristics of the drug' and 'Drug elimination in the cultured species' data (Figure 9). Recommended enthalpies of vaporization for antibiotics, pesticides and disinfectants are provided in the right bottom corner of the spreadsheet, which might be used when the required information is not available. Introduce a first-order photolysis rate coefficient for the

compound in water if the half-life of the compound in water has not been calculated under the full radiation intensities expected in the simulated scenario, otherwise, type zero.

DRUG PARAMETERS (A) Compound: **Oxytetracycline**

Physico-chemical characteristics of the drug

M	Relative molecular mass of the substance	460.44	g/mol
K _{ow}	Octanol/water partition coefficient of the substance	0.0603	(-)
k _{oc}	Sorption coefficient of the substance on organic carbon	102600	L/kg
SOL (T _{ref})	Solubility of the substance in water at reference temperature	1000	mg/L
T _{ref,SOL}	Reference temperature at which SOL(T _{ref}) was determined	20	°C
ΔH _{SOL}	Enthalpy of dissolution	25000	J/mol
VP(T _{ref})	Saturated vapour pressure of the substance at reference temperature	1.29E-19	mPa
T _{ref,VP}	Reference temperature at which VP(T _{ref}) was determined	25	°C
ΔH _p	Enthalpy of vaporization ^a	145140	J/mol
DT50 _{water}	Half-life degradation of the substance in water	9	d
T _{ref,w}	Reference temperature at which DT50 _{water} was determined	20	°C
k _{photolysis}	First-order photolysis rate coefficient in water ^b	0	1/d
DT50 _{sediment}	Half-life degradation of the substance in sediment	32	d
T _{ref,s}	Reference temperature at which DT50 _{sediment} was determined	20	°C
E	Molar Arrhenius activation energy	65400	J/mol



Drug elimination in the cultured species

BioT _{1/2(Mref,Tref)}	Biological half-life of the drug in the cultured species	2	d
W _{ref,BioT1/2}	Individual's weight at which BioT _{1/2(Mref,Tref)} was determined	0.205	kg
T _{ref,BioT1/2}	Temperature at which BioT _{1/2(Mref,Tref)} was determined	27	°C

^a Recommended values: ΔH_p

Compound	Enthalpy of vaporization
Antibiotics	97000 J/mol
Disinfectants	31700 J/mol
Pesticides	97000 J/mol

^b Set to zero if the DT50_{water} has been calculated under light conditions

Figure 9
Drug A spreadsheet of ERA-AQUA v2.0.

Open the 'Drug B' spreadsheet and fill in the 'Toxicity data for the cultured species', 'Toxicity data for non-target aquatic organisms', 'Food safety data' and 'Toxicity data for mammals' (Figure 10). When toxicity data or food safety data is not available please type NA. Please remember that the 'Toxicity data for mammals' is only required when an ADI is not available, and in this case a zero must be typed in the ADI's input cell. Default extrapolation and assessment factors for the calculation of safe concentrations are displayed in bold text.

DRUG PARAMETERS (B) Compound: **Oxytetracycline**

Toxicity data for the cultured species

EC50 _{cultured-species}	Concentration that affects 50% of the test organisms, cultured species (mortality or growth inhibition)	10	mg/L
AF _{cultured-species}	Assessment factor for short-term effect assessment on the cultured species	10	(-)

Toxicity data for non-target aquatic organisms

EC50 _{acute-algae}	Concentration that affects 50% of the test organisms, algae (growth inhibition)	0.3	mg/L
AF _{acute-algae}	Assessment factor for acute effect assessment of algae	100	(-)
EC50 _{acute-invertebrates}	Concentration that affects 50% of the test organisms, <i>Daphnia sp.</i> (immobilization)	102.0	mg/L
AF _{acute-invertebrates}	Assessment factor for acute effect assessment of invertebrates	100	(-)
LC50 _{acute-fish}	Concentration that kills 50% of the test organisms, fish	116.0	mg/L
AF _{acute-fish}	Assessment factor for acute effect assessment of fish	100	(-)
NOEC _{chronic-algae}	Chronic no observed effect concentration for algae (growth inhibition)	0.2	mg/L
AF _{chronic-algae}	Assessment factor for chronic effect assessment of algae	10	(-)
NOEC _{chronic}	Chronic no observed effect concentration for invertebrates, <i>Daphnia sp.</i> (reproduction or chronic toxicity test)	46.2	mg/L
AF _{chronic-invertebrates}	Assessment factor for chronic effect assessment of invertebrates	10	(-)
NOEC _{chronic-fish}	Chronic no observed effect concentration for fish (early-life stage test or chronic toxicity test)	NA	mg/L
AF _{chronic-fish}	Assessment factor for chronic effect assessment of fish	10	(-)

Food safety data

ADI	Acceptable daily intake for the drug. If it is not available, set to zero	0.03	mg/kg · d
MRL	Maximum residue limit in the cultured species	100	µg/kg

Toxicity data for mammals

NOAEL _{mammals}	No observed adverse effect level for mammals. Not needed if ADI is available		mg/kg · d
EF _{mammals}	Extrapolation factor to account for interspecies and intraspecies sensitivity differences	100	(-)








Figure 10
Drug B spreadsheet of ERA-AQUA v2.0.

5.2.2 Model output

1) Risk Assessment

In order to perform a risk assessment open the 'RiskAssessment' spreadsheet and press the Run button (green button at the top right corner of the spreadsheet). A bar will appear showing the progress of the risk assessment calculations. Once the calculations have been terminated, the risk assessment results will be displayed. Please note that the output spreadsheets tags, which previously were red, will turn green after the simulation has been terminated, indicating that a new model output is ready to be evaluated. The 'RiskAssessment' spreadsheet shows the results of the exposure and effect assessments as well as the calculated risk quotients for the targeted produce, aquatic ecosystems (acute and chronic), consumers and trade (Figure 11). Colored circles are displayed at the left side of the risk quotient values (function not available in Microsoft EXCEL 2007), which enable the user to quickly check the calculated risk for each individual assessment. A green color indicates no exceedance ($RQ < 1$), a yellow color indicates slight exceedance ($1 \leq RQ \leq 10$) and the red color indicates large exceedance ($RQ > 10$) of the predicted safe concentration. If some information is missing for a given risk assessment (e.g. PNEC not available due to missing toxicity value), a RQ cannot be calculated, and the model will display 'NA' (Not Available). In order to store the risk assessment output press the 'Generate Report' button. A report will be generated in Microsoft Word containing the input parameters used by the model for the risk assessment calculation, the results of the risk assessment, the drug concentration graphs and the drug mass balance in the aquaculture pond. For a better functioning of this option please close all your Word documents before to press the 'Generate Report' button. Please note that the 'Generate Report' button is only ready to be used (i.e., turning from red to green) after the risk assessment calculations have been performed.

RISK ASSESSMENT		Scenario: Pangasius catfish Vietnam	Compound: Oxytetracycline	
CULTURED SPECIES				
PeakPWC _{total}	1.29E-01 mg/L	PNEC _{cultured species}	1.00E+00 mg/L	RQ _{cultured species} 0.13 No Exceedance
AQUATIC ECOSYSTEMS				
Acute				
PeakPEC _{total}	1.29E-02 mg/L	PNEC _{algae}	3.42E-03 mg/L	RQ _{algae} 3.76 Exceedance
PeakPEC _{total}	1.29E-02 mg/L	PNEC _{invertebrates}	1.02E+00 mg/L	RQ _{invertebrates} 0.01 No Exceedance
PeakPEC _{total}	1.29E-02 mg/L	PNEC _{fish}	1.16E+00 mg/L	RQ _{fish} 0.01 No Exceedance
Chronic				
TWA _{3 total}	2.23E-03 mg/L	PNEC _{algae}	1.83E-02 mg/L	RQ _{algae} 0.12 No Exceedance
TWA _{21 total}	1.53E-03 mg/L	PNEC _{invertebrates}	4.62E+00 mg/L	RQ _{invertebrates} 0.00 No Exceedance
TWA _{28 total}	1.35E-03 mg/L	PNEC _{fish}	No PNEC mg/L	RQ _{fish} No PNEC NA
CONSUMERS				
EDI	1.24E-05 mg/kg · d	ADI	3.00E-02 mg/kg · d	RQ _{consumers} 0.00 No Exceedance
TRADE				
PCC _{harvest}	7.82E+00 µg/kg	MRL	1.00E+02 µg/kg	RQ _{trade} 0.08 No Exceedance

Figure 11

RiskAssessment spreadsheet of ERA-AQUA v2.0.

2) Drug concentration graphs and values

After the risk assessment calculations are terminated, the concentration dynamics of the drug the pond water layer, pond sediment, cultured species body mass and in the environment (i.e., watercourse receiving effluent discharges) are displayed in the 'DrugConcentrations' spreadsheet (Figure 12). Furthermore, the peak concentration of the drug sorbed to suspended solids and freely dissolved in the pond water and in the environment are shown, as well as the time weighted average concentrations in the environment. These concentrations allow the user to perform refined risk assessments with the dissolved concentration of the drug in water or the concentration of the drug sorbed to suspended solids in the water layer (see Sections 4.1 and 4.2 for a detailed explanation). Please bear in mind that the model calculates ecological risks by using the total drug concentration in the water phase by default.

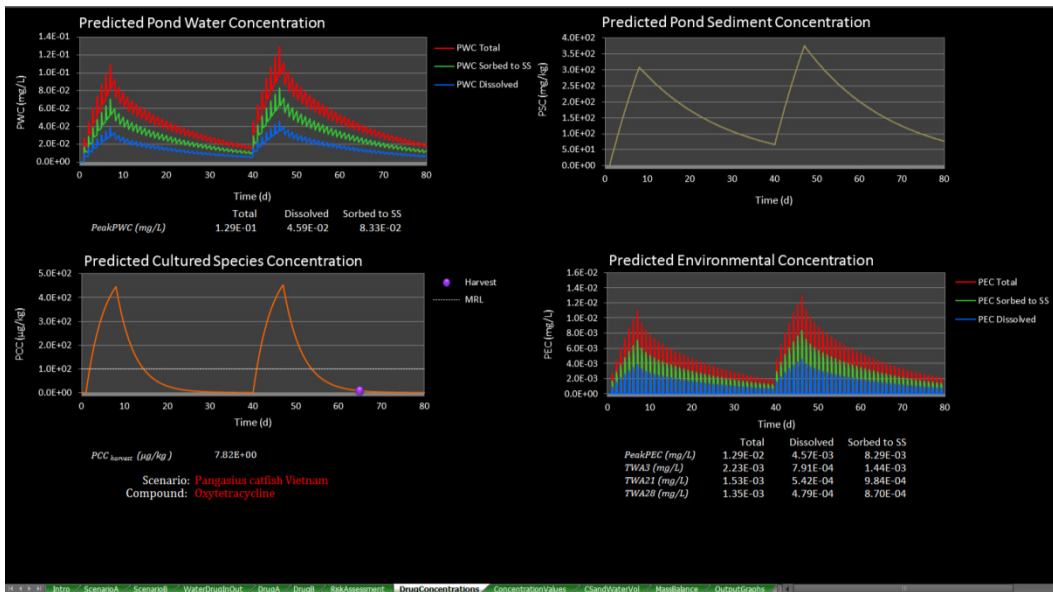


Figure 12
DrugConcentrations spreadsheet of ERA-AQUA v2.0.

In the 'ConcentrationValues' spreadsheet, the concentration values calculated by the model are shown. These values are the ones used by the model to build the graphs displayed in the 'Drug concentrations' spreadsheet. The 'ConcentrationValues' spreadsheet is unprotected, which allows the user to easily copy and transfer the data to other computer programs for further analysis. Please note that the drug fate calculations performed by the model are made for time steps of one minute but only the concentrations at time steps of one hour are showed in this spreadsheet for simplicity.

3) *Cultured species mass and water dynamics*

In the spreadsheet called 'CSandWaterVol' the cultured species mass, number of individuals, individual's organism weight, and the pond water volume dynamics over the simulation period are depicted in four graphs. These graphs allow the user to get a better understanding on the potential interactions between the cultured species mass balance, the water balance and the calculated drug concentrations. The values calculated by the model for each of these parameters are shown at the left side of the spreadsheet. Please note that calculations are performed by the model for a time step of one minute but only the values for time intervals of one hour are given in the spreadsheet.

4) *Mass balance*

The 'MassBalance' spreadsheet offers a summary of the drug mass balance in the aquaculture pond system by comparing: A) the system drug mass losses during the whole simulation period plus the remaining drug mass in the system at the end of the simulation period, and B) the drug mass input into the pond system by drug application plus the drug mass input via irrigation water. The difference between these two is calculated (A-B) as well as the mass balance error, which is calculated as the absolute value of:

$$\text{Mass balance error} = \frac{A - B}{B} \cdot 100$$

The two tables below the System Mass Balance table offer a detailed description of the drug mass losses in each compartment during the simulation period and the remaining drug mass in the pond compartments at the end of the simulation period. Furthermore, these results are expressed in two bar charts in order to allow a more quickly interpretation of the main processes influencing the drug losses in the aquaculture pond. The top bar chart depicts the percentage of the input drug mass (B) that is lost from the pond system due to different dissipation or drug transfer processes. The bottom bar chart depicts the percentage of the input drug mass (B) that remains in each compartment of the aquaculture pond at the end of simulation period.

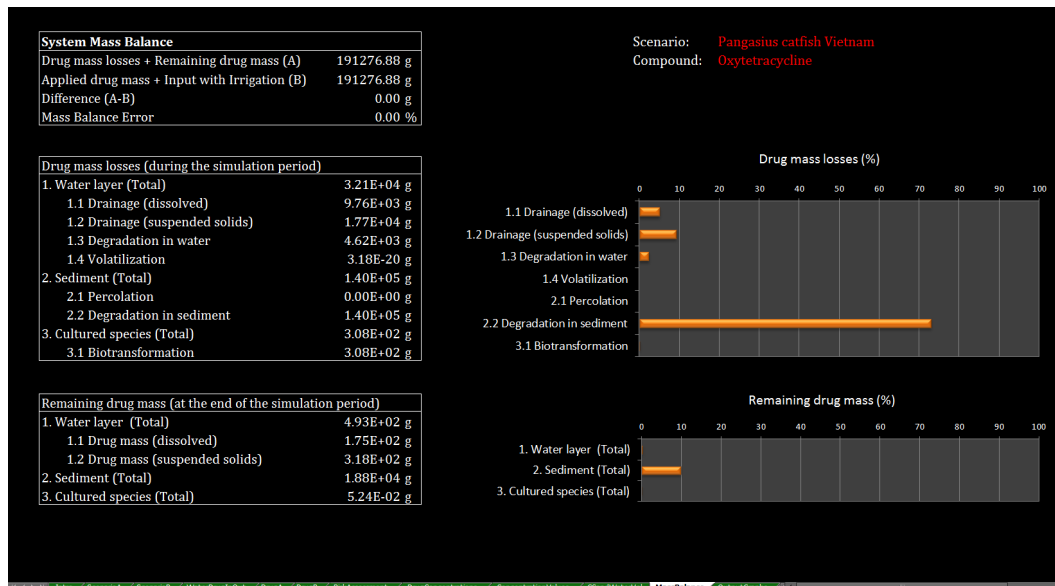


Figure 13
MassBalance spreadsheet of ERA-AQUA v2.0.

5) Output graphs

The 'OutputGraphs' spreadsheet contains an unprotected copy of the graphs that are displayed in the 'DrugConcentrations' and 'CSandWaterVol' spreadsheets. The graphs in the 'OutputGraphs' spreadsheet can be easily exported to other computer programs.

6 List of input and calculated parameters

6.1 Input scenario parameters

Aquaculture pond

A = area of the pond (m^2)

$EVAP$ = average daily evaporation rate (m/d)

f_{om} = mass fraction of organic matter in sediment (-)

$h_{pond-water}$ = (initial) depth of the water layer in the aquaculture pond (m)

$h_{pond-sediment}$ = depth of the top sediment layer in the aquaculture pond (m)

$m_{om,ss}$ = mass fraction of organic matter in suspended solids (g/g)

$PERC$ = average daily water percolation rate (m/d)

$RAIN$ = average daily rainfall rate (m/d)

ss = mass concentration of suspended solids in pond water (kg/L)

T = average ambient temperature in the modeled scenario ($^{\circ}C$)

ρ = sediment bulk density (kg/L)

ϕ = sediment porosity (v/v). Function of sediment texture: sand, sandy-loam, loam, clay-loam, silty-clay, clay. Assumed to be the same as θ_{sat} = saturated water content of the pond sediment (v/v)

Watercourse

b = bottom width of water body in the watercourse (m)

$h_{watercourse}$ = depth of the water layer in the watercourse (m)

s = side slope, horizontal/vertical, in the watercourse (-)

$v_{watercourse}$ = flow velocity in the watercourse (m/s)

Cultured species

$MORT$ = mortality fraction during the culture cycle (-)

w_{max} = maximum organism weight (kg)

ρ_{CH2} = lipid fraction of cultured organisms (-)

w_o = organism weight at the start of the simulation period (kg)

γ_o = water absorption-excretion coefficient (kg^{κ}/d) (Default value = 4200)

ρ_{CH2} = lipid layer permeation resistance ($d \cdot kg^{-\kappa}$) (Default value = 97)

ρ_{cs} = cultured species density at the start of the simulation period (kg/m^2)

ρ_{H2O} = partial water layer diffusion resistance to and from water ($d \cdot kg^{-\kappa}$) (Default value = 0.0068)

$\rho_{H2O,food}$ = partial water layer diffusion resistance to and from food ($d \cdot kg^{-\kappa}$) (Default value = 0.0002)

Feed input to the cultured species

FCR = feed conversion ratio in the cultured species (kg food/ kg cultured species)

FE = fraction of eaten feed (-)

SFR = daily specific feeding rate (kg food/kg cultured species \cdot 1/d)

w_{SFR} = organism's weight at which SFR was determined (kg)

$p_{CH_2, food}$ = lipid fraction of food (-)

Consumer characteristics

bw = consumer's body weight (kg) (Default value = 60kg for adults)

$Cons$ = daily consumption of the cultured species (kg/d)

6.2 Input water exchange, drug application and culture cycle parameters

Water exchange management

$DRAIN$ = average daily water drainage rate (m/d)

IRR = average daily water supply rate (m/d)

$t_{effluent}$ = duration of the effluent discharge (h)

Drug application

C_{IRRI} = dissolved drug concentration in the irrigation water (mg/L)

D = individual drug dose applied (mg/L for drugs applied in bath treatments or mg/kg cultured species for drugs applied mixed with feed)

DA = drug administration method (0=Bath treatment; 1=Mixed with feed)

Culture cycle

$Harvest$ = Planned harvest day after the start of the simulation period (d)

$Stock$ = Planned cultured species stocking day after the start of the simulation period (d)

$Simulation$ = Duration of the simulation period (d)

6.3 Input drug parameters

Physico-chemical characteristics of the drug

$DT50_{sediment}$ = half-life degradation of the substance in sediment at reference temperature (d)

$DT50_{water}$ = half-life degradation of the substance in water at reference temperature (d)

E = molar Arrhenius activation energy (J/mol) (Default value = 65400 J/mol)

K_{oc} = sorption coefficient of the substance on organic carbon (L/kg)

k_{ow} = octanol/water partition coefficient of the substance (-)

$k_{photolysis}$ = first-order photolysis rate coefficient in water (1/d) (Set to zero if $DT50_{water}$ has been calculated under light conditions)

M = relative molecular mass of the substance (g/mol)

$SOL(T_{ref})$ = solubility of the substance in water at reference temperature (mg/L)

T_{refs} = reference temperature at which $DT50_{sediment}$ was determined (°C)

T_{refSOL} = reference temperature at which $SOL(T_{ref})$ was determined (°C)

T_{refVP} = reference temperature at which VP was determined (°C)

T_{refw} = reference temperature at which $DT50_{water}$ was determined (°C)

$VP(T_{ref})$ = saturated vapor pressure of the substance at reference temperature (mPa)

ΔH_p = enthalpy of vaporization (J/mol) (Default value: pesticides and antibiotics = 97000 J/mol, disinfectants: 31700 J/mol)

ΔH_{SOL} = enthalpy of dissolution (J/mol) (Default value = 25000 J/mol)

Drug elimination in the cultured species

$BioT_{1/2(Mref, Tref)}$ = biological half-life of the drug in the cultured species calculated for a reference cultured species mass and temperature (d)

$W_{ref, BioT_{1/2}}$ = organism's weight at which $BioT_{1/2(Mref, Tref)}$ was determined (kg)

$T_{ref, BioT_{1/2}}$ = temperature at which $BioT_{1/2(Mref, Tref)}$ was determined ($^{\circ}C$)

Toxicity data for the cultured species

$AF_{cultured-species}$ = assessment factor for short-term effect assessment on the cultured species (Default value = 10)

$EC50_{cultured-species}$ = concentration that affects 50% of the test organisms, cultured species (mortality or growth inhibition, in mg/L)

Toxicity data non-target aquatic organisms

$AF_{acute-algae}$ = assessment factor for acute effect assessment of algae (Default value = 100)

$AF_{acute-fish}$ = assessment factor for acute effect assessment of fish (Default value = 100)

$AF_{acute-invertebrates}$ = assessment factor for acute effect assessment of invertebrates (Default value = 100)

$AF_{chronic-algae}$ = assessment factor for chronic effect assessment of algae (Default value = 10)

$AF_{chronic-fish}$ = assessment factor for chronic effect assessment of fish (Default value = 10)

$AF_{chronic-invertebrates}$ = assessment factor for chronic effect assessment of invertebrates (Default value = 10)

$EC50_{acute-algae}$ = concentration that affects 50% of the test organisms, algae (growth inhibition in mg/L)

$EC50_{acute-invertebrates}$ = concentration that affects 50% of the test organisms, Daphnia (immobilization in mg/L)

$LC50_{acute-fish}$ = concentration that kills 50% of the test organisms, fish (mg/L)

$NOEC_{chronic-algae}$ = chronic no observed effect concentration for algae (growth inhibition in mg/L)

$NOEC_{chronic-fish}$ = chronic no observed effect concentration for fish (early-life stage test or chronic toxicity test, mg/L)

$NOEC_{chronic-invertebrates}$ = chronic no observed effect concentration for invertebrates, Daphnia magna (reproduction or chronic toxicity test, mg/L)

Food safety data

ADI = acceptable daily intake for the drug (mg/kg · d). If it is not available, set to zero.

MRL = maximum residue limit in the cultured species ($\mu\text{g}/\text{kg}$)

Toxicity for mammals

$EF_{mammals}$ = extrapolation factor to account for interspecies and intraspecies extrapolation (Default value = 100)

$NOAEL_{mammals}$ = no observed adverse effect level for mammals (mg/kg · d)

6.4 Constant parameters

$k_G^{H_2O}$ = mass transfer coefficient of H_2O in air (constant parameter = 720 m/d)

$k_L^{CO_2}$ = mass transfer coefficient of CO_2 in water (constant parameter = 4.8 m/d)

M_{CO_2} = relative molecular mass of CO_2 (constant parameter = 44 g/mol)

M_{H_2O} = relative molecular mass of H_2O (constant parameter = 18 g/mol)

$q_{T;c}$ = temperature correction factor (constant parameter = 1 kg/kg)

T_{refDw} = reference temperature at which $D_w(T_{refDw})$ was determined (constant parameter = 25 $^{\circ}C$)

l = characteristic length scale (constant parameter = 0.05 cm)
 K = rate exponent (constant parameter = 0.25)
 R = universal gas constant (constant parameter ≈ 8.3144 J/mol \cdot K)

6.5 Calculated parameters

ADI = acceptable daily intake of the drug (mg/kg \cdot d) (Calculated if ADI is not available)
 $A_{watercourse}$ = cross section of the water layer in the watercourse (m²)
 $D_w(T)$ = aqueous diffusivity of the substance in water at the scenario temperature (cm²/d)
 $D_w(T_{refw})$ = aqueous diffusivity of the substance in water at 25°C (cm²/d)
 EDI = estimated daily intake of the drug (mg/kg \cdot d)
 f_{oc} = mass fraction of organic carbon in sediment (-)
 $k_{absorption}$ = absorption rate constant of the substance in the cultured species (L/kg \cdot d)
 $k_{assimilation}$ = drug assimilation rate constant in the cultured species ($\frac{\mu\text{g} \cdot \text{kg cultured species}^{-1}}{\mu\text{g} \cdot \text{kg food}^{-1}} \cdot 1/d$)
 $k_{cs-growth}$ = cultured species growth rate constant (1/d)
 k_d = sediment/water partitioning coefficient of the substance (L/kg)
 $k_{desorption}$ = first-order desorption rate coefficient (1/d)
 $k_{egestion}$ = drug egestion rate constant (1/d)
 $k_{elimination(M,T)}$ = normalized total drug elimination rate constant in the cultured species (1/d)
 $k_{elimination(Mref,Tref)}$ = total drug elimination rate constant in the cultured species calculated for a specific cultured species mass and temperature (1/d)
 $k_{excretion}$ = drug excretion rate constant (1/d)
 K_H = dimensionless Henry coefficient of the substance (-)
 $k_{mortality}$ = mortality rate constant (1/d)
 K_{om} = sorption coefficient on organic matter (L/kg)
 $k_s(T)$ = first-order degradation rate coefficient of the substance in sediment at ambient temperature (1/d)
 $k_s(T_{refs})$ = first-order degradation rate coefficient of the substance in sediment at reference temperature (1/d)
 $k_{transformation}$ = drug biotransformation rate constant (1/d)
 $k_{volatilization}$ = mass transfer coefficient of the substance from water to atmosphere at ambient temperature (m/d)
 $k_w(T_{refw})$ = first-order degradation rate coefficient of the substance in water at reference temperature (1/d)
 $k_w(T)$ = first-order degradation rate coefficient of the substance in water at ambient temperature (1/d)
 M_{CS} = cultured species mass (kg)
 N_{ind} = number of individuals in the aquaculture pond (-)
 N_{indo} = number of individuals in the aquaculture pond at the start of the simulation period (-)
 p_1 = fraction of ingested food assimilated (kg cultured species/kg food)
 PCC = predicted cultured species concentration ($\mu\text{g}/\text{kg}$)
 $PCC_{harvest}$ = predicted drug concentration in the cultured species at harvest ($\mu\text{g}/\text{kg}$)
 $Peak\ PEC_{diss}$ = highest momentary dissolved predicted environmental concentration (mg/L)
 $Peak\ PEC_{ss}$ = highest momentary predicted environmental concentration of the drug sorbed to suspended solids (mg/L)
 $Peak\ PEC_{total}$ = highest momentary total predicted environmental concentration (mg/L)
 $Peak\ PWC_{total}$ = highest momentary predicted total pond water concentration during the simulation period (mg/L)
 PEC_{diss} = predicted dissolved environmental concentration (mg/L)
 PEC_{ss} = predicted environmental concentration of the drug sorbed to suspended solids (mg/L)
 PEC_{total} = predicted total environmental concentration (mg/L)
 $PNEC_{acute-fish}$ = acute predicted no effect concentration for fish (mg/L)
 $PNEC_{acute-invertebrates}$ = acute predicted no effect concentration for invertebrates (mg/L)
 $PNEC_{chronic-algae}$ = chronic predicted no effect concentration for algae (mg/L)
 $PNEC_{chronic-fish}$ = chronic predicted no effect concentration for fish (mg/L)

$PNEC_{chronic-invertebrates}$ = chronic predicted no effect concentration for invertebrates (mg/L)
 $PNEC_{cultured-species}$ = predicted no effect concentration for the cultured species (mg/L)
 PSC = predicted pond sediment concentration (mg/kg)
 PWC_{diss} = predicted dissolved pond water concentration (mg/L)
 PWC_{ss} = predicted concentration of the drug in the pond water sorbed to suspended solids (mg/L)
 PWC_{total} = predicted total drug concentration in the pond's water (mg/L)
 $Q_{effluent}$ = effluent flow (L/s)
 $Q_{watercourse}$ = water flow in the watercourse (L/s)
 $RQ_{acute-algae}$ = acute risk quotient for algae (-)
 $RQ_{acute-fish}$ = acute risk quotient for fish (-)
 $RQ_{acute-invertebrates}$ = acute risk quotient for invertebrates (-)
 $RQ_{chronic-algae}$ = chronic risk quotient for algae (-)
 $RQ_{chronic-fish}$ = chronic risk quotient for fish (-)
 $RQ_{chronic-invertebrates}$ = chronic risk quotient for invertebrates (-)
 $RQ_{consumers}$ = risk quotient for consumers (-)
 $RQ_{cultured-species}$ = risk quotient for the cultured species (-)
 RQ_{trade} = risk quotient for trade (-)
 $SOL(T)$ = solubility of the substance in water at ambient temperature (mg/L)
 $TWA_{21} total$ = total time weighted average concentration for invertebrates (mg/L)
 $TWA_{28} total$ = total time weighted average concentration for fish (mg/L)
 $TWA_3 total$ = total time weighted average concentration for algae (mg/L)
 $VP(T)$ = saturated vapor pressure of the substance at ambient temperature (mPa)
 w = organism weight (kg)
 γ_1 = food ingestion coefficient (kg^κ/d)
 γ_2 = biomass production coefficient (kg^κ/d)

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Appendix I

Enthalpies of vaporization (ΔH_p ; kJ/mol) for antibiotics (average: 99.5; SD: 21.3) and disinfectants (average: 31.7; SD: 19.9) commonly used in Asian aquaculture:

Antibiotic	ΔH_p (kJ/mol)	Antibiotic	ΔH_p (kJ/mol)	Antibiotic	ΔH_p (kJ/mol)
Chloramphenicol	99.98	Enrofloxacin	88.70	Oxytetracycline	145.14
Chlortetracycline	125.11	Florfenicol	96.27	Sulfamethoxazole	74.70
Ciprofloxacin	91.50	Norfloxacin	88.90	Tetracycline	120.61
Doxycycline	105.53	Oxolinic acid	77.57	Trimethoprim	80.02

Disinfectant	ΔH_p (kJ/mol)	Disinfectant	ΔH_p (kJ/mol)	Disinfectant	ΔH_p (kJ/mol)
Acetic acid	23.7	Formaldehyde	23.3	Iodine	20.75
Chlorine	10.2	Hydrogen peroxide	51.5	Triclosan	61.19

Enthalpies of dissolution (ΔH_{sol} ; kJ/mol) for disinfectants (average: 25.3; SD: 32.9) used in Asian aquaculture:

Disinfectant	ΔH_{sol} (kJ/mol)	Disinfectant	ΔH_{sol} (kJ/mol)
Acetic acid	-1.50	Hydrogen peroxide	-3.50
Formaldehyde	62.00	Potassium permanganate	44.00



Alterra is part of the international expertise organisation Wageningen UR (University & Research centre). Our mission is 'To explore the potential of nature to improve the quality of life'. Within Wageningen UR, nine research institutes – both specialised and applied – have joined forces with Wageningen University and Van Hall Larenstein University of Applied Sciences to help answer the most important questions in the domain of healthy food and living environment. With approximately 40 locations (in the Netherlands, Brazil and China), 6,500 members of staff and 10,000 students, Wageningen UR is one of the leading organisations in its domain worldwide. The integral approach to problems and the cooperation between the exact sciences and the technological and social disciplines are at the heart of the Wageningen Approach.

Alterra is the research institute for our green living environment. We offer a combination of practical and scientific research in a multitude of disciplines related to the green world around us and the sustainable use of our living environment, such as flora and fauna, soil, water, the environment, geo-information and remote sensing, landscape and spatial planning, man and society.

More information: www.alterra.wur.nl/uk