ALGORITHM OF CALCULATION OF PREDICTED NO-EFFECT CONCENTRATION (PNEC) FOR EVALUATION OF THE ENVIRONMENTAL RISK OF VETERINARY MEDICINAL PRODUCTS

ALGORITM DE CALCUL AL CONCENTRAȚIEI PREDICTIBILE FĂRĂ EFECT (PNEC) PENTRU EVALUAREA RISCULUI DE MEDIU AL PRODUSELOR MEDICINALE VETERINARE

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Rezumat

Analiza riscului de mediu pentru produsele medicinale veterinare este o evaluare a posibilei lor evoluții, a modului de actiune , a efectelor produse și este structurată in două faze, în conformitate cu ghidurile VICH GL6 (faza I) și GL38 (faza II). Evaluarea riscurilor de mediu, parte integrantă a autorizațiilor pentru produsele medicinale veterinare , interpretată conform ghidurilor VICH, asigură predictibilitatea și transparența rezultatelor obținute. Calea de distribuție și evoluția în mediu a substanței active din produsul medicinal veterinar sunt factori importanți pentru evaluarea efectului expunerii finale. Concentrația predictibilă fără efect (PNEC) este concentrația unei substanțe în orice mediu sub care efectele adverse nu se vor produce, cel mai probabil pe durata expunerii pe termen lung sau pe termen scurt. În evaluarea riscului pentru mediu, valorile PNEC vor fi comparate cu concentrația predictibilă de mediu (PEC) pentru a determina dacă riscul unei substanțe este acceptabil sau nu. Dacă PEC / PNEC <1, riscul este acceptabil. PNEC-urile sunt de obicei calculate prin raportarea descriptorilor de doză toxicologică la un factor de evaluare. Punctele finale utilizate cel mai frecvent pentru determinarea PNEC-urilor sunt mortalitatea (concentrația medie letală, LC50), creșterea / dezvoltarea somatică (concentrația efectivă, ECx sau concentrația fără efecte observate, NOEC) și reproducerea (concentrația efectivă, ECx sau concentrația fără efecte observate, NOEC). Se determină PNEC-urile pentru factorii de mediu: apă, sediment și sol. În lucrare se prezintă un algoritm de calcul al concentrațiilor predictibile fără efect (PNEC) pentru factorii de mediu: sol, apa, sediment. Aceste calcule sunt necesare pentru evaluarea riscului de mediu pentru produselor medicinale veterinare. Pe baza acestui algoritm de calcul, a fost elaborat un software original, interactiv specializat , care să permită determinarea rapidă și convenabilă a concentrațiilor predictibile fără efect, PNEC, pentru factorii de mediu: sol, apă, sedimente pentru produsele medicinale veterinare. Softul este un instrument foarte util pentru specialiștii în evaluarea riscurilor de mediu.

Abstract

The environmental risk analysis for veterinary medicinal products is an assessment of their possible evolution, exposures and effects and is structured according to the VICH GL6 (Phase I) and GL38 (Phase II) guides. The environmental risk assessment, an integral part of the veterinary medicinal product authorizations, interpreted and harmonized under the VICH guidelines, ensures the predictability and transparency of the results obtained. The route of distribution and the evolution in the environment are important factors for the concentration of the final exposure. Predicted No-Effect Concentration (PNEC) is the concentration of a substance in any environment below which adverse effects will most likely not occur during long term or short term exposure. In environmental risk assessment, PNECs will be compared to predicted environmental concentration (PEC) to determine if the risk of a substance is

acceptable or not. If PEC/PNECs<1, the risk is acceptable. The PNECs are usually calculated by dividing toxicological dose descriptors by an assessment factor. The endpoints most frequently used for deriving PNECs are mortality (LC50), growth (ECx or NOEC) and reproduction (ECx or NOEC). PNECs need to be derived for various environmental compartments (water, sediment, soil, air, etc.). The paper presents an algorithm for calculating predictable no-effect concentrations (PNEC) for environmental factors: soil, water, sediment required for environmental risk assessment of veterinary medicinal products. Based on this calculation algorithm, specialized interactive software has been developed to allow rapid and convenient determination of predictable no-effect concentrations, PNEC, for environmental factors: soil, water, sediment for veterinary medicinal products. It is a very useful tool for environmental risk assessment specialists.

Introduction

Risk assessment is an evaluation of the possible fate, exposure and effects of the product. As a whole, the risk assessment is structured around the risk quotient approach as described in VICH guidelines GL6 (Phase I) and GL38 (Phase II).

The risk quotient (RQ) is defined as the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC).

The risk quotients indicate the likelihood of adverse effects occurring.

The Phase II assessment starts at Tier A with a base data set on fate and effects that allows for risk characterisation.

The PNECs are usually calculated by dividing toxicological dose descriptors by an assessment factor.

The endpoints most frequently used for deriving PNECs are mortality (LC_{50}), growth (ECx or NOEC) and reproduction (ECx or NOEC).

Assessment factors (AFs) are used to address the differences between laboratory data and natural conditions, taking into account of interspecies differences and intra-species differences.

Assessment factors applied for long-term tests are smaller because the uncertainty of the extrapolation from labs to natural environment is reduced.

More data on more species in the same environmental compartment can also reduce uncertainties, thus further decreasing assessment factors.

Usually PNECs are only derived for 4 compartments:

- fresh water,
- soil,
- STP micro-organism and
- sediment.

In the absence of any eco-toxicological data for soil organisms or sediment-dwelling organisms, the PNEC-soil and PNEC-sediment may be provisionally calculated from PNEC-water using the equilibrium partitioning method (EPM) (Table 1).

EPM is usually not recommended for substances that may pose a high hazard potential to soil organisms (i.e., logKow / Koc >5 and LC_{50}/EC_{50} to <1mg/L to aquatic species) [2, 3, 4].

Table 1.

Assessment factors used for PNEC calculation (from ECHA guidance on chemical risk assessment) [2].

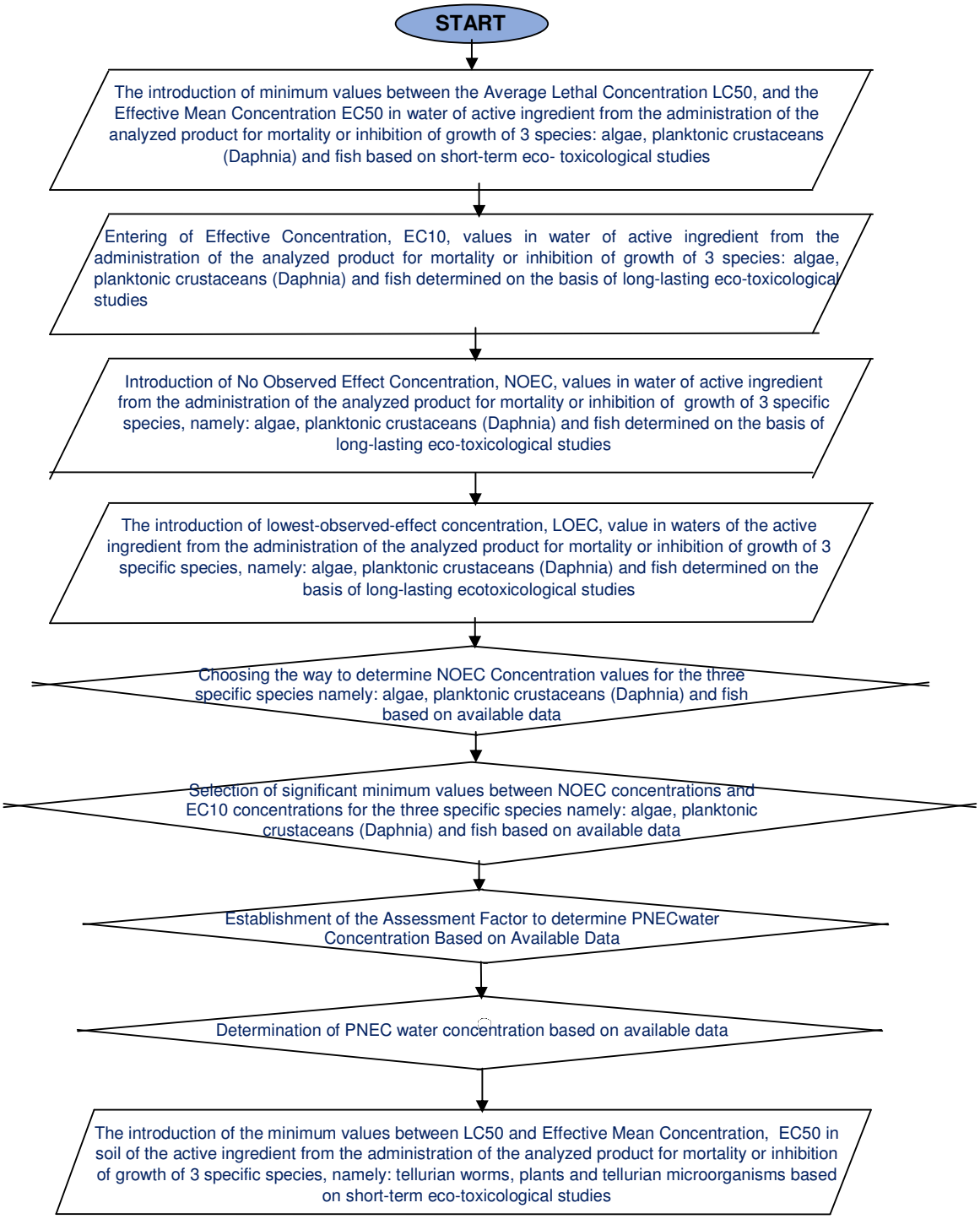
PNEC Type	Available Data	AFs
PNEC-*water* or PNEC *soil*	At least one short term L(E)C50 from each of three trophic levels	1000
	One long-term EC10 or NOEC from one trophic level	100
	Two long-term results (e.g. EC10 or NOECs) from species representing two trophic levels	50
	Long-term results (e.g. EC10 or NOECs) from at least three species representing three trophic levels	10
	Species sensitivity distribution (SSD) method	1-5
	Field data or model ecosystems	Case by case
PNEC-*STP micro-organism*	Short-term EC50 from activated sludge respiratory inhibition	100
	Long-term NOEC from activated sludge respiratory inhibition or biodegradability test	10
	Long-term NOEC from inhibition of nitrification bacteria	1
PNEC-*sediment*	One long term test (NOEC or EC10) on one sediment living organism	100
	Two long-term test (NOEC or EC10) with two species of sediment living organism	50
	Three long-term test (NOEC or EC10) with three species of sediment living organism	10

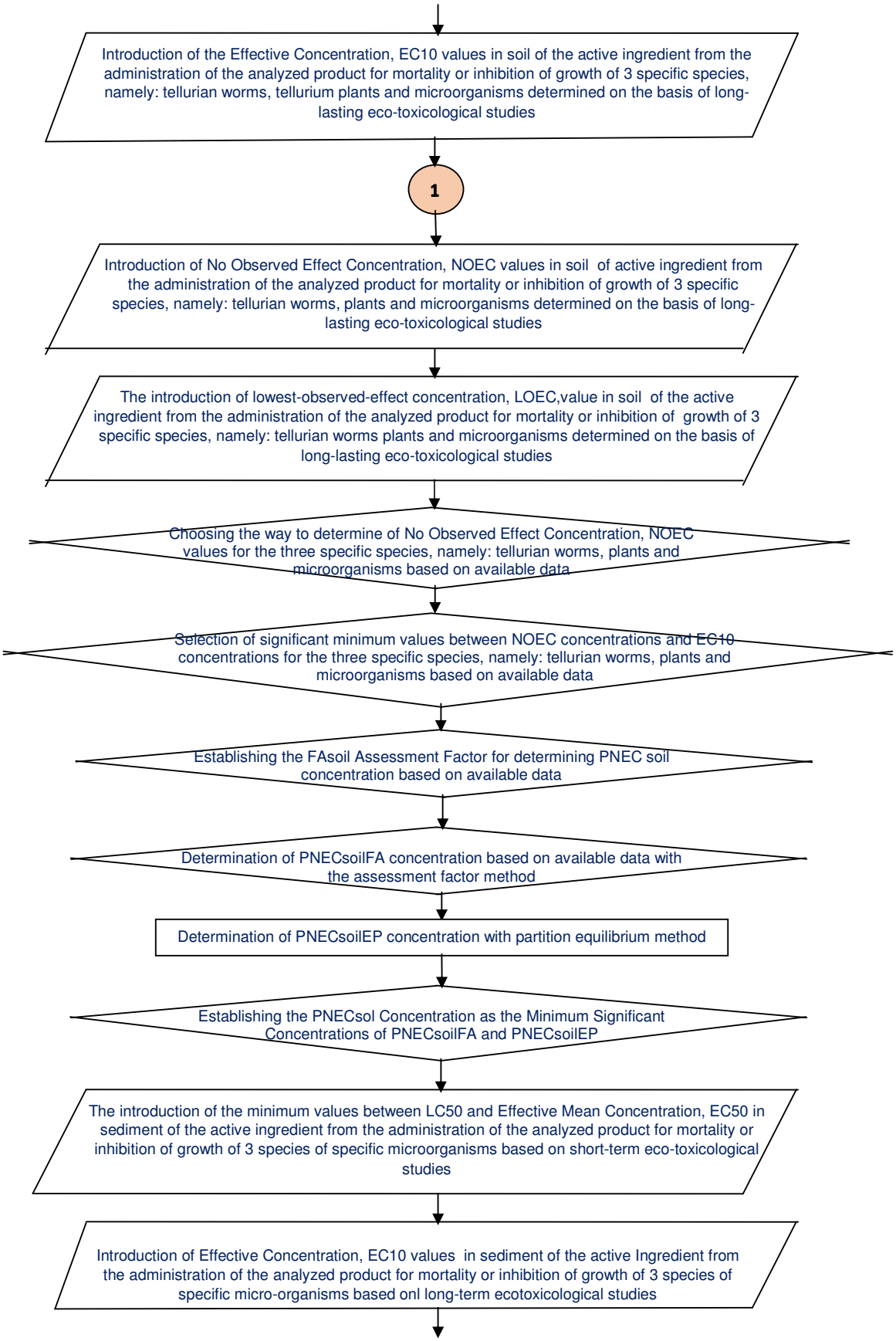
2. Algorithm of calculation for predicted no-effect concentration (PNEC)

The paper presents an algorithm for calculating predictable no-effect concentrations (PNEC) for environmental factors: soil, water, sediment required for environmental risk assessment of veterinary medicinal products.

Based on this calculation algorithm, a specialized interactive and original software has been developed to allow rapid and convenient determination of predictable no-effect concentrations, PNEC, for environmental factors: soil, water, sediment for veterinary medicinal products (fig. 1).

It is a very useful tool for environmental risk assessment specialists.




Introduction of the Effective Concentration, EC10 values in soil of the active ingredient from the administration of the analyzed product for mortality or inhibition of growth of 3 specific species, namely: tellurian worms, tellurium plants and microorganisms determined on the basis of long-lasting eco-toxicological studies
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Introduction of No Observed Effect Concentration, NOEC values in soil of active ingredient from the administration of the analyzed product for mortality or inhibition of growth of 3 specific species, namely: tellurian worms, plants and microorganisms determined on the basis of long-lasting eco-toxicological studies
The introduction of lowest-observed-effect concentration, LOEC,value in soil of the active ingredient from the administration of the analyzed product for mortality or inhibition of growth of 3 specific species, namely: tellurian worms plants and microorganisms determined on the basis of long-lasting eco-toxicological studies
Choosing the way to determine of No Observed Effect Concentration, NOEC values for the three specific species, namely: tellurian worms, plants and microorganisms based on available data
Selection of significant minimum values between NOEC concentrations and EC10 concentrations for the three specific species, namely: tellurian worms, plants and microorganisms based on available data
Establishing the FAsoil Assessment Factor for determining PNEC soil concentration based on available data
Determination of PNECsoilFA concentration based on available data with the assessment factor method
Determination of PNECsoilEP concentration with partition equilibrium method
Establishing the PNECsol Concentration as the Minimum Significant Concentrations of PNECsoilFA and PNECsoilEP
The introduction of the minimum values between LC50 and Effective Mean Concentration, EC50 in sediment of the active ingredient from the administration of the analyzed product for mortality or inhibition of growth of 3 species of specific microorganisms based on short-term eco-toxicological studies
Introduction of Effective Concentration, EC10 values in sediment of the active Ingredient from the administration of the analyzed product for mortality or inhibition of growth of 3 species of specific micro-organisms based onl long-term ecotoxicological studies

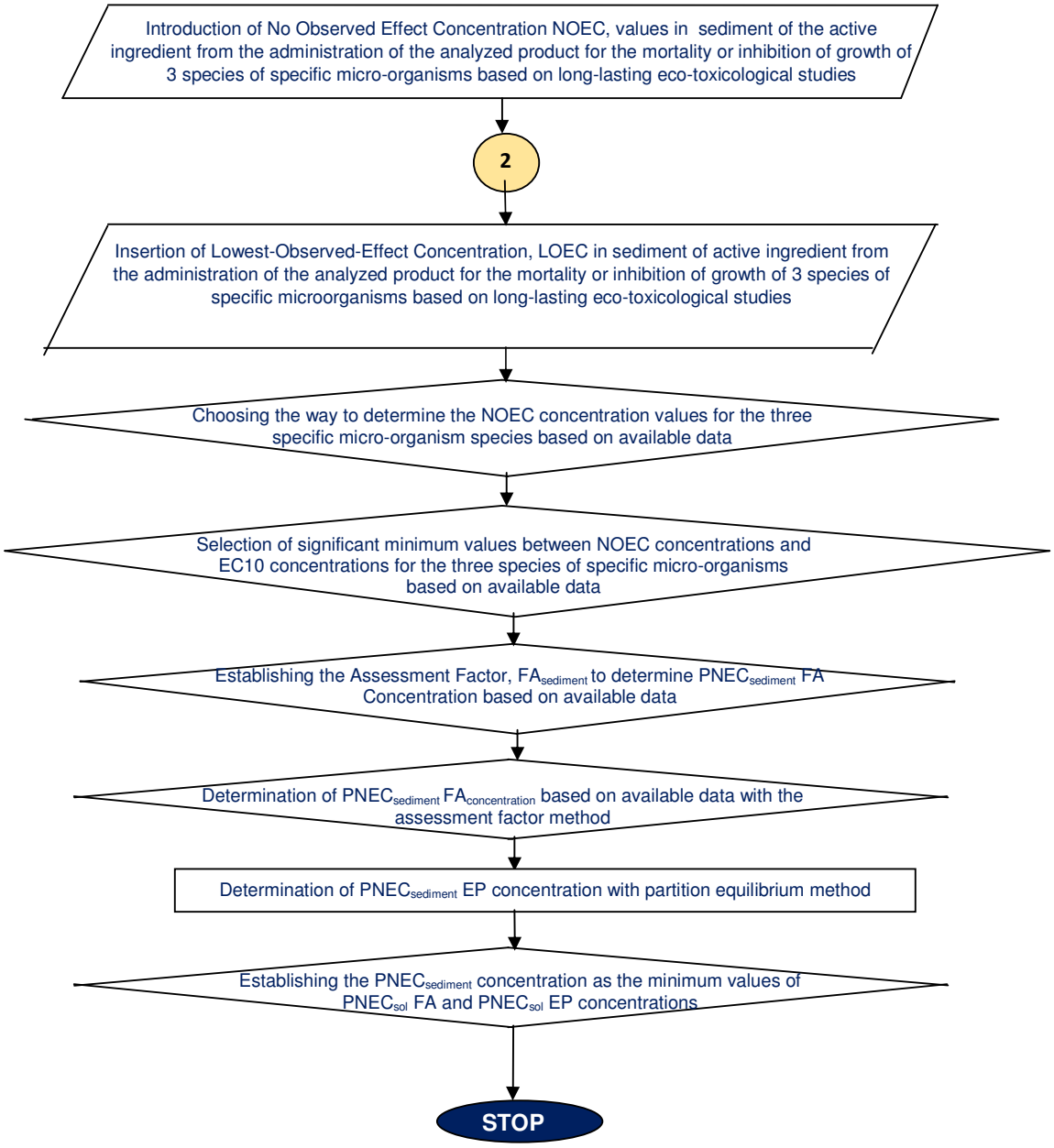

Figure 1. Software Appearance for $PNEC_{water}$ [mg /dmc],
Predictable No Effect Concentration on active ingredient on administration of analyzed product

$$PNECapa := \begin{cases} \frac{\min(LEC50alge, LEC50crustacee, LEC50pesti)}{FAapa} & \text{if } (LEC50alge \neq 0 \wedge LEC50crustacee \neq 0 \wedge LEC50pesti \neq 0) \wedge (NOECal = 0 \wedge NOECcr = 0 \wedge NOECpe = 0) \\ \frac{NOECal}{FAapa} & \text{if } NOECal \neq 0 \wedge NOECcr = 0 \wedge NOECpe = 0 \\ \frac{NOECcr}{FAapa} & \text{if } NOECal = 0 \wedge NOECcr \neq 0 \wedge NOECpe = 0 \\ \frac{NOECpe}{FAapa} & \text{if } NOECal = 0 \wedge NOECcr = 0 \wedge NOECpe \neq 0 \\ \frac{\min(NOECal, NOECcr)}{FAapa} & \text{if } NOECal \neq 0 \wedge NOECcr \neq 0 \wedge NOECpe = 0 \\ \frac{\min(NOECal, NOECpe)}{FAapa} & \text{if } NOECal \neq 0 \wedge NOECcr = 0 \wedge NOECpe \neq 0 \\ \frac{\min(NOECcr, NOECpe)}{FAapa} & \text{if } NOECal = 0 \wedge NOECcr \neq 0 \wedge NOECpe \neq 0 \\ \frac{\min(NOECal, NOECcr, NOECpe)}{FAapa} & \text{if } NOECal \neq 0 \wedge NOECcr \neq 0 \wedge NOECpe \neq 0 \\ 0 \text{ otherwise} \end{cases}$$

$$PNECapa = 0.1$$

It is to note that:

- the algorithm allows consideration to be given to all species and categories of animals, intensive breeding technologies or pastures that are treated concomitantly with a particular veterinary medicinal product;
- the algorithm allows consideration to be given to the class of a particular veterinary medicinal product and the treatment characteristics (daily doses of the active ingredient, duration of treatment);
- the algorithm requires matrix calculation as a veterinary medicinal product can be administered concomitantly to several species and categories of animals, intensive farming or grassland technologies;
- intensive growth and pastures are taken into account the species and categories of animals mentioned in the guide.
- species and animal categories are matrix elements (row species and column categories) used to express the matrix calculation.

Conclusions

Based on this computational algorithm, an original interactive specialized software has been developed to allow rapid and convenient determination of Predicted No-Effect Concentration (PNEC) for environmental factors: soil, water, sediment for veterinary pharmaceuticals. It is a very useful tool for environmental risk assessment specialists.

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