

## Algorithm of calculation of predicted concentration (pec) for evaluation of the environmental risk of veterinary medicinal products

### Algoritm de calcul al concentrațiilor predictibile (PEC) pentru evaluarea riscului de mediu la produse medicinale veterinare

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**Key words:** environment, PEC, algorithm

**Cuvinte cheie:** mediu, PEC, algoritm

#### 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. 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. For the determination of PECs, soil, water, sediment, environmental exposure for the product, its active substances and other ingredients is considered, taking into account target species, mode of administration, and physicochemical characteristics. Calculation of the predicted active substance concentration in the soil (PEC<sub>soil</sub>) is based on the total residue approach. The calculation of the concentration of the active substance in groundwater (PEC<sub>groundwater</sub>) is based on the solid sorption equilibrium approach, modeled by the organic water-carbon distribution coefficient (K<sub>oc</sub>). The predicted concentration of the active substance in surface water (PEC surface water) is considered to be 1/3 of the groundwater concentration and in the sediment is calculated according to the sediment-water partition coefficient (K<sub>sed-water</sub>). The paper presents an algorithm for calculating predictable concentrations for environmental factors: soil, water, sediment required for environmental risk assessment of veterinary medicinal products. Based on this calculation algorithm, a specialized interactive software has been developed to allow rapid and convenient determination of predictable PEC concentrations for environmental factors: soil, water, sediment for veterinary medicinal products. It is a very useful tool for environmental risk assessment specialists.

#### Rezumat

Analiza riscului asupra mediului pentru produsele medicinale veterinare este o evaluare a posibilei evoluții, expunerii și efectelor acestora și este structurată conform ghidurilor VICH GL6 (faza I) și GL38 (faza II). Evaluarea riscului asupra mediului, parte integrantă din dosarele de autorizare a produselor medicinale veterinare, interpretată și armonizată în conformitate cu ghidurile VICH, asigură predictibilitatea și transparența rezultatelor obținute. Calea de distribuție și evoluția în mediu sunt factori importanți pentru concentrația expunerii finale. Coeficientul de risc (RQ) este definit ca raportul dintre concentrația predictibilă în mediu (PEC) și concentrația predictibilă fără efect (PNEC) și indică probabilitatea efectelor adverse care se produc. Pentru determinarea PEC-urilor sol, ape, sediment, se analizează expunerea la mediu pentru produs, substanțele sale active și alte ingrediente, luând în considerare speciile țintă, modul de administrare, și caracteristicile fizico-chimice. Calculul concentrației predictibile de substanță activă din produsul medicinal în sol (PEC<sub>sol</sub>) se face pe baza abordării rezidului total. Calculul concentrației de substanță activă în ape freatică (PEC<sub>ape freatică</sub>) se face pe baza abordării echilibrului de sorbție în solide, modelată prin coeficientul de distribuție apă-carbon organic (K<sub>oc</sub>). Concentrația predictibilă de substanță activă în apele de suprafață (PEC<sub>ape de suprafață</sub>) se consideră 1/3 din concentrația în ape freatică iar în sediment se calculează funcție de coeficientul de partiție sediment-apă (K<sub>sed-apa</sub>). Lucrarea prezintă un algoritm de calcul al concentrațiilor predictibile PEC pentru factorii de mediu: sol, ape, sediment necesar pentru evaluarea riscurilor de mediu pentru produsele medicinale veterinare. Pe baza acestui algoritm de calcul a fost realizat un soft-ware specializat interactiv care permite determinarea rapidă și comodă a concentrațiilor predictibile PEC pentru factorii de mediu: sol, ape, sediment pentru produsele medicinale veterinare. Acesta se constituie într-un instrument deosebit de util specialiștilor pentru evaluarea riscurilor de mediu.

## 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.

In Phase I, the determination of PECs soil, water, sediment analyzes the potential extent of exposure to the environment for the product, its active substances and other ingredients, taking into account target species, mode of administration, and physicochemical characteristics.

Calculation of PEC soil for intensively-grown animals is dependent on the amount of active residue contained in landfilled manure.

According to the EUROSTAT database, a nitrogen load of 170 kg N / ha is on average the maximum load in most EU countries.

Calculation of PEC soil for livestock is dependent on the number of animals kept in any place on the land surface.

This parameter is known as storage density and is expressed in animals per hectare.

The route of distribution and the environmental evolution of active substances in veterinary medicinal products are important for the concentration of final exposure.

In the case of veterinary medicinal products, the predominant routes of exposure for the terrestrial and aquatic environment are through direct excretion, manure management as a fertilizer and leakage and accidental spillage of liquid manure from zootechnical farms.

The predicted concentration of the active substance in the medicinal product in the soil ( $PEC_{sol}$ ) is based on the total residue approach, considering that the total active

substance dose applied is excreted by the animal without taking into account data on metabolism and excretion.

The calculation of the concentration of the active substance in groundwater ( $PEC_{groundwater}$ ) is based on the solid sorption equilibrium approach, modeled by the organic water-carbon distribution coefficient ( $K_{oc}$ ).

In calculating the concentration of active substance in surface waters, it is assumed that part of the discharged water will be diluted with two parts of water.

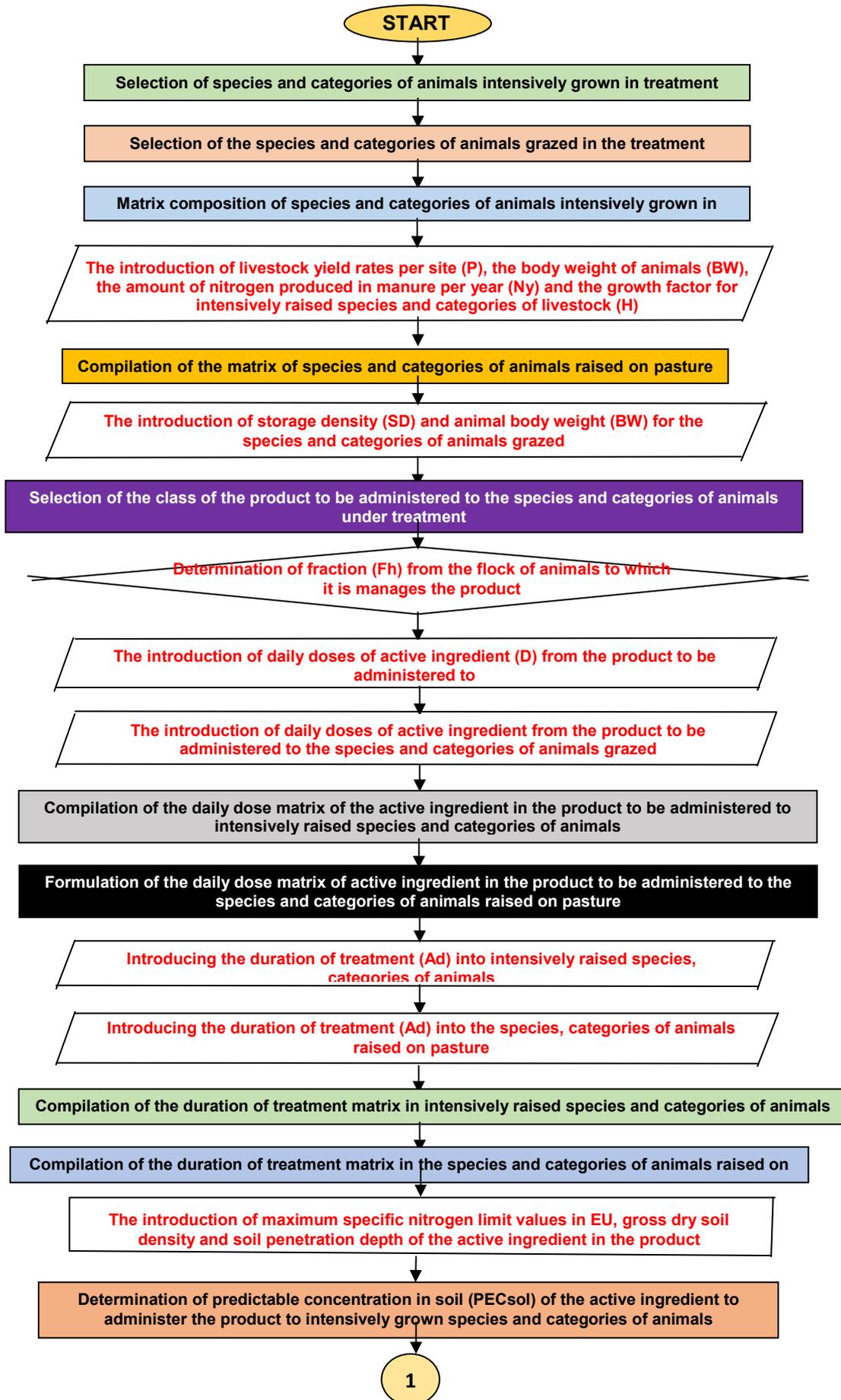
Thus, the predicted concentration of the active substance in surface waters ( $PEC_{surface\ waters}$ ) is considered to be 1/3 of the predictable concentration in the groundwater and in the sediment ( $PEC_{sediment}$ ) is calculated according to the sediment-water partition coefficient ( $K_{sed-water}$ ).

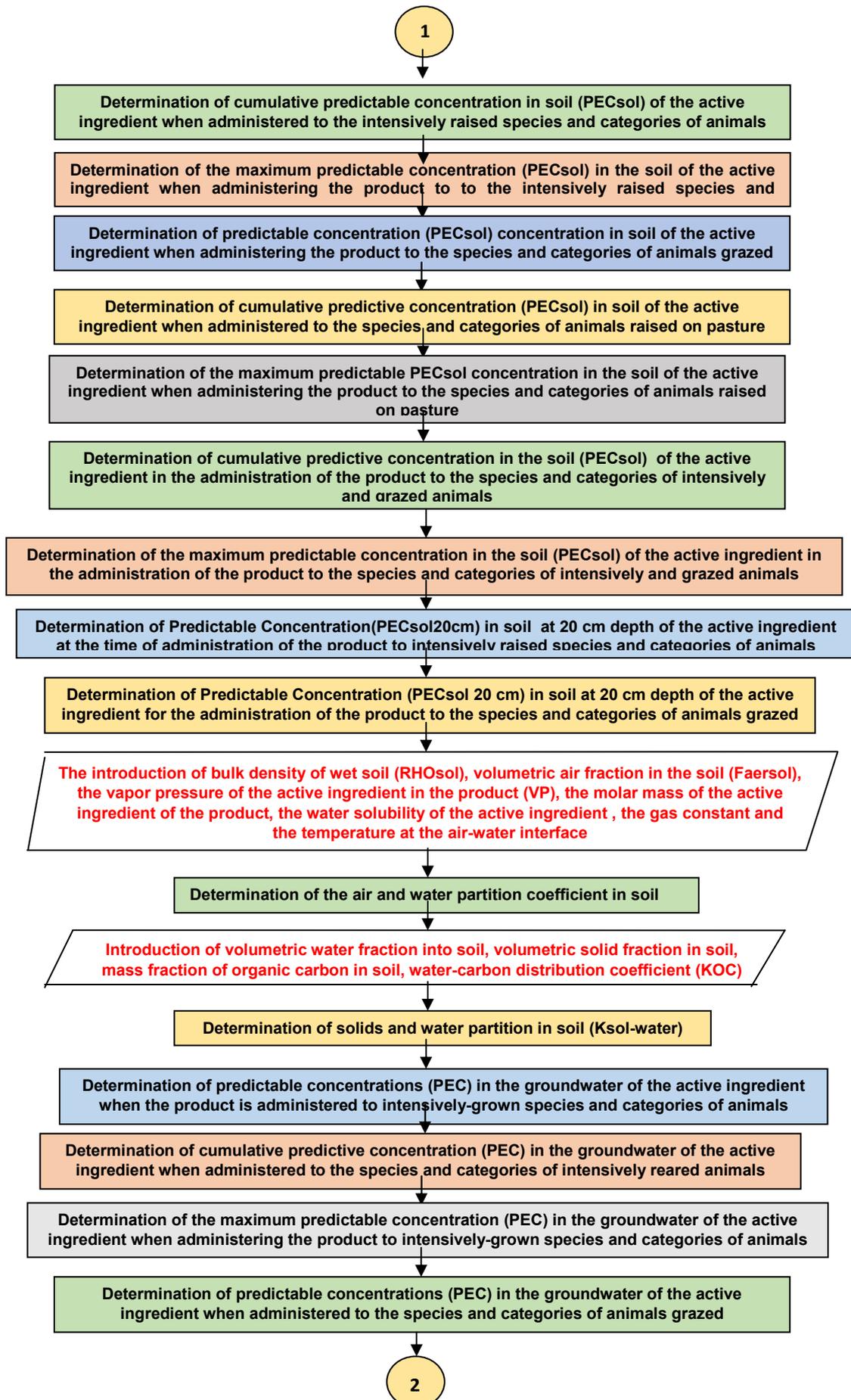


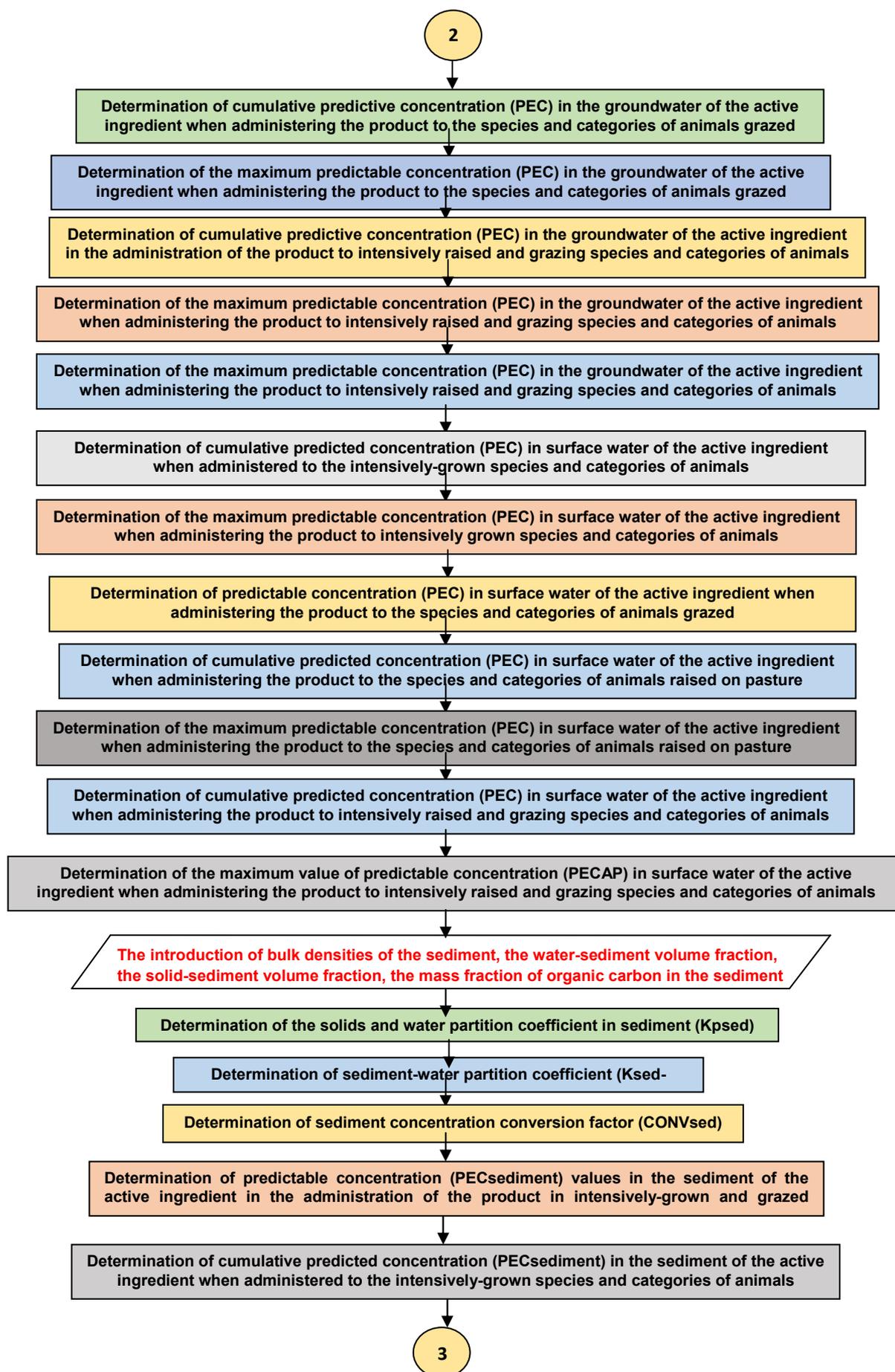
Source: <https://www.canstockphoto.com/earth-in-hands-grass-background-18899229.html> [2].

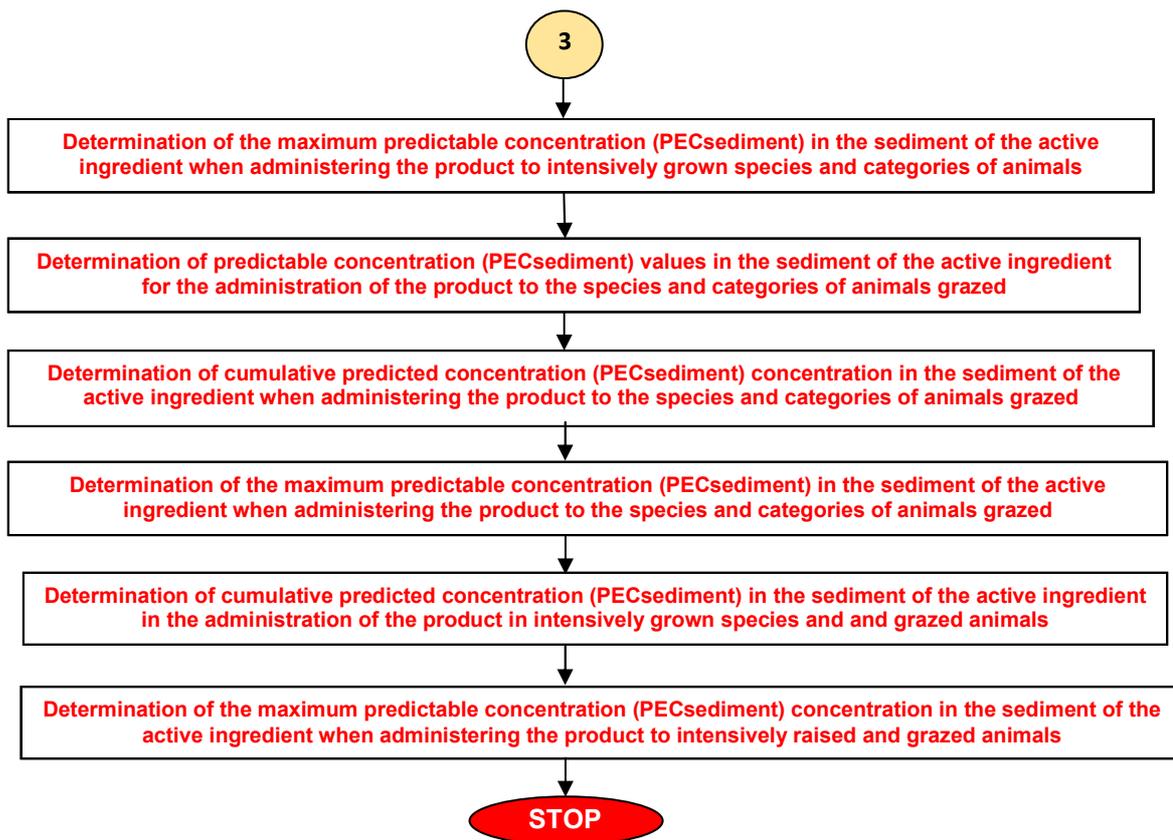
### Algorithm of calculation for Predicted environmental concentration (PEC)

In the following is presented an algorithm for calculating predictable PEC concentrations for environmental factors: soil, water, sediment ( $PEC_{sol}$ ,  $PEC_{ground\ water}$ ,  $PEC_{surface\ water}$ ,  $PEC_{sediment}$ ) required for the environmental risk assessment of the veterinary medicinal products in Phase I, phase in which a 100% release of the active ingredient in the medium will normally be undertaken (total residue approach).









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 pharmaceutical product;
- the algorithm allows consideration to be given to the class of a particular pharmaceutical product and the treatment characteristics (daily doses of the active ingredient, duration of treatment);
- the algorithm requires matrix calculation as a pharmaceutical 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.

$$\begin{matrix}
 \text{PEC}_{\text{solinitiali}} = & \begin{pmatrix} 59.976 & 44.956 & 70.519 & 81.6 & 0 & 0 \\ 91.233 & 82.507 & 29.292 & 0 & 0 & 0 \\ 44.348 & 5.181 & 9.822 & 2.792 & 22.1 & 30.959 \\ 36.061 & 0 & 0 & 0 & 0 & 0 \\ 36.267 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \\
 \text{PEC}_{\text{solinitialp}} = & \begin{pmatrix} 39.2 & 58.52 \\ 16.8 & 12.6 \\ 33.6 & 17.5 \\ 12.6 & 0 \\ 23.1 & 0 \end{pmatrix}
 \end{matrix}$$

Fig. 1. Results for PEC initial soil (intensive and pasture) obtained in matrix form in soft, corresponding to the species and categories of treated animals.

$$\begin{matrix}
 \text{PEC}_{\text{Capedesuprafatai}} = & \begin{pmatrix} 66.394 & 49.767 & 78.065 & 90.333 & 0 & 0 \\ 100.997 & 91.336 & 32.427 & 0 & 0 & 0 \\ 49.094 & 5.735 & 10.873 & 3.091 & 24.465 & 34.272 \\ 39.92 & 0 & 0 & 0 & 0 & 0 \\ 40.148 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \\
 \text{PEC}_{\text{Capedesuprafatap}} = & \begin{pmatrix} 43.395 & 64.783 \\ 18.598 & 13.948 \\ 37.196 & 19.373 \\ 13.948 & 0 \\ 25.572 & 0 \end{pmatrix}
 \end{matrix}$$

Fig. 2. The results for PEC surface waters (intensive and pasture) obtained in the form matrix software, corresponding to the treated species and categories of animals.

$$\text{PEC}_{\text{sediment}} = \begin{pmatrix} 361.053 & 270.63 & 424.518 & 491.228 & 0 & 0 \\ 549.22 & 496.686 & 176.338 & 0 & 0 & 0 \\ 266.972 & 31.189 & 59.129 & 16.809 & 133.041 & 186.374 \\ 217.083 & 0 & 0 & 0 & 0 & 0 \\ 218.324 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$\text{PEC}_{\text{sedimentp}} = \begin{pmatrix} 235.982 & 352.288 \\ 101.135 & 75.851 \\ 202.27 & 105.349 \\ 75.851 & 0 \\ 139.061 & 0 \end{pmatrix}$$

Fig.3. The results for sediment PEC (intensive and pasture) obtained in the form matrix software, corresponding to the species and categories of animals treated.

## Conclusions

Based on this computational algorithm, an interactive specialized software has been developed to allow rapid and convenient determination of predictable PEC concentrations for environmental factors: soil, water, sediment for veterinary pharmaceuticals. It is a very useful tool for environmental risk assessment specialists.

## References

1. Guide EMEA/CVMP/ERA/418282 /2005-Rev1.
2. <https://www.canstockphoto.com/earth-in-hands-grass-background-18899229.html>