RISK ASSESSMENT MODELS FOR THE PREDICTION OF THE LEVELS OF RESIDUES OF VETERINARY MEDICINES IN THE ENVIRONMENT

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Veterinary medicines (VMs) licensed within the European Union (EU) must satisfy relevant scientific criteria on quality, efficacy and safety. With regard to safety, animals, consumers and those handling the product have traditionally been of primary importance. More recently, environmental safety has become an issue of both public and regulatory concern.

In the EU, Commission Directive 92/18/EEC outlines the requirements for the environmental risk assessment of VMs. Specifically, all products must be assessed for potential environmental impact. The assessment process covers two phases. In the first phase (Phase I), the level of environmental exposure is considered.

Residues of VMs can enter the environment by a number of exposure scenarios. For example, grazing animals may excrete the product directly onto pasture and in turn residues can enter the soil.

Pivotal to the exposure assessment in Phase I is the calculation of the Predicted Environmental Concentration (PEC). The PEC gives an estimate of the level of exposure for a given scenario and is thus essential for an initial indication of negative impact. Should the PEC exceed some defined critical value, then a Phase II assessment must be undertaken, for example, if the PEC in soil exceeds 10 μg/kg , a phase II assessment is required.

A number of models have been developed to assist pharmaceutical companies and regulatory bodies in the calculation of the PEC (for example Spaepen *et al* (1997)[1]). Individual models focus on particular environmental exposure scenarios, and are both product and treatment location specific. The parameter values included in these models are deterministic in nature and therefore do not account for uncertainty or variability in the variables being modelled. Uncertainty and variability are, however, important in the real life situation. In this paper, the use of stochastic models for the PEC calculation is considered.

Materials and Methods

The use of stochastic models is considered for environmental exposure resulting from direct excretion of the product in the urine and faeces of treated animals. Thus it is assumed that treated animals are grazing pasture and that the product has been internally applied. For such a scenario, the PEC in soil is given by the following equation

$$PEC = \frac{N \times ID \times BW \times T \times F_m \times 1000}{W_s + W_u}$$

This equation is formulated in terms of both product and farm/animal specific parameters. Product specific parameters include ID (mg / kg body weight), the individual treatment dose rate, T, the number of treatments per year and F_m, the fraction of the total administered dose which corresponds to the residue of interest. Inclusion of the parameter F_m accounts for the fact that the residue of interest may be the parent substance, a metabolite or a transformation product of the treatment product. For the farm/animal specific parameters, N is the stocking density per hectare, BW (kg) is the mean body weight, W_s (kg / hectare) is the weight of the soil and W_u (kg / hectare / year) is the weight of the urine excreted onto pasture.

As in the procedure presented by Spaepen *et al* (1997)[1], the weight of the soil W_s is calculated as the product of the soil volume V (m^3 / hectare) and bulk density r (kg / m^3). It is assumed that all residues entering the soil, that is from both urine and faeces, are evenly distributed in the top 5cm of the soil (CVMP Guidelines)[2]. Hence, it is assumed that animals will move uniformly over the pasture during the full year and $V = 500$. The soil bulk density r will depend on soil texture which will in turn depend on location. A value of 1,500 kg/m^3 is used as recommended in the CVMP Guidelines[2] and hence $W_s = 750{,}000$.

It is assumed that all urine excreted onto pasture will directly enter the soil. In contrast, it is assumed that faeces do not enter the soil. Whether or not faecal output will enter the soil will depend on weather conditions and soil types, for example, in wet weather faeces are very likely to become mixed with soil while in dry weather such mixing would be unlikely. The model could easily be modified to account for different degrees of faeces and soil mixing.

For any animal species urine output is likely to be dependent on body weight. It is assumed that this dependency is described by the following relationship

$$W_u = \frac{U_d \times BW \times 365 \times N}{1000}$$

where U_d (ml / kg body weight / animal / day) is the output of urine. This function assumes that animals graze pasture for the full year. If this is not the case then urine output should be reduced by multiplying by the proportion of the year during which animals graze.

Deterministic and stochastic calculations of the PEC were undertaken for the anthelmintic fenbendazole (Panacur ™) which is used for the treatment of nematode infections in sheep. The parameters used are shown in Table (1). In both the deterministic and stochastic models, the parameters ID, W_s, T and F_m take their pre-defined constant values. The remaining parameters N, BW and WU are described by mean values in the deterministic model. The uncertainty in the mean values is described by probability distributions in the stochastic model. The mean values and uncertainty distributions were derived from expert opinion and the literature. The stochastic model was formulated in the @RISK (© Palisade) software package and results obtained are for 1000 iterations.

Parameter	Deterministic Model	Stochastic Model
BW	70 kg	Normal(70,7) kg
ID	5 mg / kg body weight	5 mg / kg body weight
N	11 animals	Pert(7,11,15) animals
F_m	0.8	0.8
W_s	750,000 kg	750,000 kg
U_d	40 ml / kg body weight / day	40 ml / kg body weight / day

Table 1: Parameter values used in the deterministic and stochastic models

Results

For the deterministic model the estimated PEC for fenbendazole is 8.09 μg/kg. European regulations state that the estimated PEC in soil must exceed 10 μg/kg for a Phase II assessment to be required. Consequently, a Phase II assessment would not be required if the mean value were to be used as an estimate of exposure.

The results for the stochastic model give an interval of uncertainty for the mean PEC. In particular, it is 90% certain that the mean PEC is between 5.81 μg/kg and 10.65 μg/kg. Consequently it could be concluded that a Phase II assessment may be required.

Discussion

In this paper, the idea of using stochastic models for the calculation of the PEC has been introduced and for the simple case described, it has been shown that inclusion of uncertainty can generate different conclusions from those obtained from the deterministic model. In particular, deterministic results conclude that a Phase II assessment is not required while results from the stochastic model suggest that this may not always be the case. Consequently, trigger values may be exceeded and further assessments required.

The model and example results presented here are simple in nature and are currently being updated. More specifically, the effect of residue degradation in soil is being modelled. In addition inclusion of both uncertainty and variability in model parameters is being undertaken. However, even from these simple results the inclusion of uncertainty and variability would seem important in the decision making process.

Reference

1. Spaepen K R I, Van Leeput J J, Wislocki P G and Verschueren C (1997) A uniform procedure to estimate the predicted environmental concentration of the residues of veterinary medicines in soil. Environmental Toxicology and Chemistry 9, 1977-1982

2. European Agency for the Evaluation of Medicinal Products, Committee for Veterinary Medicinal Products. 1996. Note for guidance: Environmental risk assessment for veterinary medicinal products other than CMO-containing and immunological products. EMEAICVMP/055196, London, UK.