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Guideline on assessing the toxicological risk to human health and groundwater communities from veterinary pharmaceuticals in groundwater

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Executive summary

Groundwater is a source of human drinking water and also provides a very unique ecosystem with vulnerable aquatic communities. This guideline provides a methodology for performing a risk assessment of groundwater for human health and aquatic ecosystems for veterinary medicinal products. A risk assessment needs to be performed when the concentration of a VMP in groundwater is equal to, or above 0.1 µg/l. In addition, this guideline specifies cases where a risk assessment may be needed for highly toxic or persistent substances, when the predicted concentration in groundwater is lower than 0.1 µg/l. The guideline complements existing guidelines such as the CVMP guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL 6 and GL 38. These guidelines provide a methodology for risk assessment of veterinary medicines, but for groundwater they only provide a methodology for exposure assessment.

1. Introduction and legal background

The need for an assessment of veterinary medicinal products (VMPs) in groundwater is included in the VICH GL 38 “Environmental Impact Assessment for Veterinary Medicinal Products Phase II” (VICH 2005) and the CVMP guideline *“Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38”* (EMA, 2016), referred to as the CVMP Technical Guidance Document (TGD). This guideline gives further technical support to the implementation of the VICH guidelines GL6 (VICH 2000) and GL38 (VICH 2005) on the environmental risk assessment (ERA) of VMPs. As part of the ERA, the predicted environmental concentration (PEC) in groundwater of a veterinary medicine needs to be compared against the value of 0.1 µg/l. The value of 0.1 µg/l is the groundwater quality standard (GQS) for pesticides and biocides according to the Groundwater Directive 2006/118/EC (GWD), Annex I. Up to now, and based on the recommendations in the CVMP TGD (EMA, 2016) the CVMP has followed the approach below:

- Concentrations above 0.1 µg/l have been considered unacceptable for all substances, regardless of their intrinsic hazardous properties. In this situation, applicants could refine the PEC groundwater with additional data (e.g., modelling, more studies e.g. on degradation in manure, mitigation measures), or, if this was not possible, restrictions to the proposed uses were required to avoid predicted values equal to or above 0.1 µg/l.
- For concentrations below 0.1 µg/l, no risk was anticipated and no further regulatory action was required.

When this value of 0.1 µg/l was introduced into the European groundwater legislation as a GQS, it was established as a precautionary limit value as this was the usual limit of detection of these kinds of substances in water (with concentrations below this limit being difficult to quantify due to analytical limitations). Consequently, predicted concentrations below 0.1 µg/l were interpreted as equivalent to ‘no emission into groundwater’, thus concluding that any obligation to prevent entry of hazardous substances into groundwater was fulfilled. However, analytical methods are continuously improving with the result that it is now often possible to quantify substances below the current limit value of 0.1 µg/l. Thus, the limit value is no longer guided by the limit of detection, and in certain situations additional considerations might be appropriate for substances for which concentrations have been detected or predicted below this value. This is especially the case when their safe concentration in water is significantly lower than this limit value of 0.1 µg/l.

It is also important to consider that the current Article 6(1) of the GWD mandates that all Member States shall take measures to prevent the input into the groundwater compartment of substances listed in points 1 to 6 of Annex VIII of the Water Framework directive (2000/60/EC) (so called, 'zero-tolerance substances'). Annex I of the GWD also lays down GQS for entry into groundwater of plant protection products, biocides and their metabolites. This Directive, however, does not contain any specific provisions for VMPs nor for those active ingredients in VMPs that are also active ingredients in pesticides or biocides. For example, certain VMPs contain the same substances as pesticides or biocides or meet the definitions of hazardous substances according to Annex VIII of Directive 2000/60/EC, e.g. organohalogens.

The Phase II ERA guideline for VMPs (VICH, 2005) notes that 'groundwater is a natural resource and should not only be assessed with regards to public health but also to possible harmful effects to the biota of groundwater'. The guideline, however, does not provide any further information on how to assess possible harmful effects to human health or ecosystems, i.e., when the predicted concentration in groundwater is estimated to be ≥0.1 µg/l and for situations where the predicted safe concentrations (i.e., predicted no effect concentration (PNEC)) for the aquatic compartment is below the value of 0.1 µg/l. For certain VMPs the PNECs are below 0.1 µg/l and a review of environmental quality standards (EQS) for surface waters (values similar to PNEC values) has revealed that the safe annual average concentration could be three or more orders of magnitude lower than the GQS of 0.1 µg/l (UK TAG, 2012). For example, the EQS for annual average concentrations of the substance cypermethrin in surface waters is $8*10^{-5}$ µg/l (Directive 2013/39/EU as regards priority substances in the field of water policy). The taxa that are specifically sensitive to these kinds of compounds are also present in groundwater. Thus, this example shows that a universal groundwater quality standard of 0.1 µg/l may not be viewed as a safe value for all surface water and groundwater species.

2. Scope

This guideline outlines the methodology for performing a human health and environmental risk assessment for groundwater, considering:

1. The environmental and human health risk assessment approach for the groundwater compartment for substances with a predicted environmental concentration (PEC) above the GQS of 0.1 µg/l.

2. An environmental risk assessment for a substance with PEC in groundwater below 0.1 µg/l when scientific evidence indicates that concentrations below 0.1 µg/l might pose a risk to groundwater ecosystems (for instance, if after a Phase II assessment, based on the aquatic PNEC it can be foreseen that the $PNEC_{groundwater}$ will be lower than 0.1 µg/l).

When determining the potential impact of a VMP on groundwater, consideration has to also be given by the applicant to relevant European Union legislation on groundwater. In view of this, the CVMP considers that substances that come within the scope of points 1 to 6 of Annex VIII to the WFD, and active substances of VMPs that are also used as pesticides and/or biocides should be subject to the same limits, as laid down in Annex II of the GWD, i.e. that they should not enter groundwater at concentrations ≥ 0.1 µg/l.

3. Quantification of risk to humans from residues in groundwater

The risk to humans of VMPs in groundwater is associated with the use of groundwater as drinking water. The risk assessment in this guideline is therefore based on scenarios following human consumption of drinking water derived from groundwater.

In order to assess the risk of groundwater contamination by VMPs for human health a maximum tolerable concentration in drinking water (MTC_{dw}) (µg/l) needs to be calculated following the same methodology used by the World Health Organization (WHO, 2011).

$$MTCdw = \frac{ADI \times BW \times P}{Cw} \quad \text{(Equation 1)}$$

The recommended default values to be used in the calculation of the MTC_{dw} and their units are listed in Table 1.

Table 1. Recommended default values to be used in the calculation of the MTC_{dw} in Equation 1 and their units.

	Parameter description	Unit	Default value
BW	Body weight	[kg]	60
MTCdw	Maximum tolerable concentration in drinking water	[$\mu g.l^{-1}$]	–
ADI	Acceptable daily intake	[$\mu g.kg^{-1}.day^{-1}$]	–
P	Fraction of the ADI to be used by the intake of drinking water	[–]	0.1*
C_w	Daily consumption of drinking water	[$l.d^{-1}$]	2

* An indicative value. See text for further details

The default values of 60 kg for the weight of the human body and 2 litres for the daily consumption of drinking water are based on the recommendations made by WHO and used within the WHO methodology. Any deviation from the default values in Table 1 needs to be accompanied by a solid scientific justification.

The CVMP establishes acceptable daily intake (ADI) values for all active ingredients for use in VMPs for administration to food producing animals. The ADI is a toxicological risk limit, which is identical to the Tolerable Daily Intake (TDI) used within, for example, the WHO terminology. It represents a toxicologically safe value even if exposure is prolonged. It is recommended to operate with 10% as an indicative maximum percentage of the ADI to be used by drinking water. However, in principle the exact fraction needs to be defined on a case by case basis as the acceptable daily intake via drinking water depends on the anticipated daily intake via other sources and hence by the established MRLs, meaning that the actual P value may in practice be higher or lower than 0.1. It is of paramount importance that the total intake of the VMP by consumers (via water and food products) does not exceed the ADI.

Based on the information on the predicted concentration in groundwater (PEC_{gw}) and the maximum tolerable concentration in drinking water (MTC_{dw}), the potential risk of the VMP to humans via drinking water can be assessed by the risk quotient in Equation 2 below.

$$\mathrm{RQ}gw = \frac{\mathrm{PEC}gw}{\mathrm{MTC}dw} \quad \text{(Equation 2)}$$

In cases where the RQ_{gw} exceeds 1.0 a potential risk for groundwater has been identified and a risk refinement needs to be done. This may include a refinement of the PEC_{gw} and/or a scientific justification for deviating from the default input parameters in the MTC_{gw} calculation. For a refinement and final establishment of the PEC_{gw} the K_{oc} and DT_{50} are typically needed in order to run the appropriate models, which are available in the ERA according to the VICH GLs.

If the RQ_{gw} is below 1.0, the risk to human health is considered acceptable.

4. Quantification of risk to groundwater ecosystems

In addition to the human health assessment, an environmental risk assessment for groundwater ecosystems is also needed. Contamination of groundwater may permanently eradicate entire unique groundwater communities due to the low or absent ability to re-colonise any affected habitats. In addition, because of the absence of primary producers in groundwater systems, the self-purification process may be disturbed and the original state cannot easily be restored.

4.1. Definition of groundwater ecosystems of concern

In the environmental risk assessment procedure according to the VICH guidelines GL6 (VICH 2000) and GL 38 (VICH, 2005), ecosystems in the aquatic compartment are defined by a few representative habitats e.g. a stream, a pond, freshwater sediment for freshwater surface ecosystems or pelagic water, and marine sediments for marine ecosystems. Probably the most representative groundwater habitats are on hypogean karst (fractures, channels, caves), and alluvial gravel interstitial systems. For the protection of the whole groundwater compartment, it is also necessary to protect spring water. Springs are an ecotone, a transition between groundwater and surface water bodies, and in this context are also considered groundwater, as they may fill gravel pits and ponds or lakes without other influx from surface water.

4.2. Environmental risk assessment considerations

The assessment of the environmental risks of VMPs is framed by internationally agreed guidelines (i.e., VICH guidelines GL6 and GL38), which prescribe the use of data from a limited number of tests on fate, behaviour and ecotoxicity of the VMP. The current guidelines do not include ecotoxicity testing for the determination of the safe concentration of a substance in water with species other than surface water species (i.e., algae, daphnids and fish species). Experimental data obtained from these three groups of organisms may be extrapolated to predict safe concentrations for highly adapted groundwater biota. However, this extrapolation is only possible when the unique biotic and abiotic conditions of groundwater ecosystems are taken into account. Any additional uncertainties should be addressed through the use of more adequate assessment factors.

The groundwater ecosystem is considered more vulnerable than many other aquatic ecosystems. The concept of ecosystem vulnerability, defined as the “exposure to contingencies and stress, and the difficulty in coping with them" (Millennium Ecosystem Assessment report, 2005), comprises three major dimensions:

i) Exposure to stress, perturbations and shocks;

ii) Sensitivity of exposed species to the stress or perturbation, including their capacity to anticipate and cope with the stress;

iii) Resilience of the exposed ecosystems, and species in terms of their capacity to absorb shocks and perturbations while maintaining function.

The 3 bullets mentioned above have been considered when determining the most appropriate assessment factors when extrapolating from data on surface water species.

4.2.1. Exposure to stress, perturbations, and shocks:

An important element to be considered for the ERA of groundwater ecosystems is the duration of exposure of chemicals to any resident communities. There are indications that groundwater ecosystems have a more prolonged period of exposure time, given that this ecosystem is generally colder than surface water systems, and this aspect combined with a complete absence of sunlight (at least in the vast majority of cases), could result in decreased biotic and abiotic degradation processes (Yagi et al., 2010; Bulog and Mali Bizjak, 2014) leading to chemical concentrations persisting longer. In most surface water systems (e.g. rivers), the residence time of water (the average amount of time that a molecule of water spends in a particular system) ranges from a few days to a few weeks. However, in groundwater ecosystems such as porous aquifers, the residence time may be decades or even centuries (Freeze and Cherry, 1979). Consequently, whereas the baseline quality of the riverine surface water may recover after a relatively short period of time, the recovery in aquifers (if any) may require decades, or disturbances may even be irreversible.

4.2.2. Sensitivity of exposed species to the stress or perturbation, including their capacity to anticipate and cope with the stress

The sensitivity of groundwater species to an acute exposure of a chemical stressor may be equivalent or higher than that of a model aquatic species used for ecotoxicity testing (Blonk, 2014). Further, the chronic effects of chemical stressors to groundwater species are not known (Blonk, 2014; van Beelen, 2007; Avramov, 2013).

Groundwater species have developed a number of metabolic adaptations for extreme energy saving to deal with starvation, for instance their metabolism is significantly lower than that of most other aquatic species. These adaptations can affect the species response to a chemical stressor, and make them more sensitive to the long term effects of chemical stressors than surface water species (Di Lorenzo et al., 2015). However, it is also important to note that the metabolic potential of groundwater species under sudden favourable conditions is higher for faster energy recovery and restoration of body reserves (Simcič et al., 2005; Hervant et al., 1997). Thus, the ability to respond to chemical stressors may be slower in groundwater species. The energetic cost of this response may cause a secondary effect on the survival and reproduction in exposed groundwater species in the long term, when compared to surface water species.

4.2.3. Resilience and complexity of groundwater ecosystems

Groundwater ecosystems are characterised by lower levels of complexity due to the allotrophy[1] and heterotrophy[2] of this system. This lower level of complexity also implies that re-colonisation after perturbation may be extremely slow, and that the restoration of an affected biotic community is unlikely (Culver and Pipan, 2009). Thus, groundwater ecosystems have low resilience to perturbations. Groundwater species are characterised by a high level of endemism, longevity, slow growth and low reproduction rates. The biological adaptations of these species contribute to the low plasticity of their community when reacting to repeated or chronic pressure due to chemical stressors.

Surface water ecosystems are characterised by a higher level of complexity, making them more able to recover from stress, mostly in the timeframe of one or few seasons.

Due to the low resilience to perturbations by groundwater ecosystems, recovery from the toxic effects of VMPs may not be possible within a realistic timeframe. Consequently, the permanent loss of endemic groundwater species is a realistic threat (Bulog and Mali Bizjak, 2014).

4.2.4. Conclusion on the use of assessment factors

The arguments presented above show that groundwater ecosystems may be more vulnerable than surface water ecosystems and may lack the ability to recover from perturbations. As a result, an additional assessment factor of 10 should be applied to extrapolate the $PNEC_{groundwater}$ from the $PNEC_{Surrfacewater}$. A similar approach based on vulnerability, complexity of ecosystems and limited data availability is already applied when extrapolating the EQS for surface waters to an EQS for “other surface waters” (i.e., pelagic marine ecosystem) within the Water Framework Directive (Directive 2013/39/EC).

$$PNEC_{groundwater} = PNEC_{surfacewater}/10$$

5. Risk assessment of groundwater ecosystems

5.1. Scenario 1: $PEC_{groundwater} \geq 0.1\ \mu g/l$

5.1.1. Exposure assessment

The initial concentration of a VMP in groundwater ($PEC_{groundwater}$) is determined using the methods described in the CVMP TGD (2016). If the initial concentration exceeds the GQS of 0.1 µg/l, the exposure can be refined. The $PEC_{surfacewater}$ is first refined using the FOCUS[3] PEARL model (Focus, 2000), using the parameters outlined in Appendix I of the CVMP TGD (2016). The exposure assessment can also be refined by determining degradation in manure in accordance with the respective CVMP guideline (EMA, 2011).

5.1.2. Risk characterisation

In Phase II of the ERA the safe concentration for surface water species is determined ($PNEC_{surfacewater}$) based on experimental ecotoxicological data. The $PNEC_{surfacewater}$ can be extrapolated to a

[1] Referring to bioproduction being largely dependent on transport of resources from the surface
[2] Referring to the need to use organic carbon for growth.
[3] FOCUS: Forum for the Coordination of Pesticide Fate Models and Their Use

$PNEC_{groundwater}$ (see chapter 4). For this extrapolation, an additional assessment factor of 10 should be considered.

$$PNEC_{groundwater} = PNEC_{surfacewater}/10$$

Using the $PNEC_{groundwater}$, the RQ for the groundwater compartment is determined.

$$RQ_{groundwater} = PEC_{groundwater}/PNEC_{groundwater}$$

If the $RQ_{groundwater}$ is ≥1 based on this initial $PEC_{groundwater}$ the applicant can propose refinement of $PEC_{groundwater}$ values according to the supporting CVMP GL (EMA 2005). The $PNEC_{groundwater}$ can also be refined, using the standard Tier B surface water tests (but still including the additional assessment factor of 10). No further refinement of $PNEC_{groundwater}$ with experimental studies on groundwater species is possible, as long as no appropriate ecotoxicological long term test for groundwater species are available.

When a risk to the groundwater is indicated, the applicant should propose adequate risk mitigation measures to protect groundwater ecosystems. If no suitable risk mitigation measure/s can be applied, the risk for groundwater has to be addressed in the benefit risk assessment.

5.2. Scenario 2: PECgroundwater < 0.1 µg/ l and PNECsurfacewater ≤ 1 µg/l derived from Tier B surface water toxicity tests

For most VMPs, the $PEC_{groundwater}$ will be ≤ 0.1 µg/l. In these situations, a risk assessment for this compartment will not be needed, unless Tier B ecotoxicity data show that the $PNEC_{surfacewater}$ is ≤ 1 g/l. In this situation, the $PNEC_{groundwater}$ would be ≤ 0.1 µg/l (i.e., $PNEC_{groundwater} = PNEC_{surfacewater}/10$), and a risk to the groundwater compartment for a compound with a concentration < 0.1 µg/l may not be excluded. In this case, $PNEC_{groundwater}$ needs to be compared to the $PEC_{groundwater}$ in order to determine if there is a possible risk to the groundwater compartment, even if the PEC groundwater is ≤ 0.1 µg/l.

When a risk to the groundwater is indicated, the applicant should propose adequate risk mitigation measures to protect groundwater ecosystems. If no suitable risk mitigation measure/s can be applied, the risk for groundwater has to be addressed in the benefit risk assessment.

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