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Are the parasiticidal avermectins resistant to dissipation in the environment? The case of eprinomectin

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ABSTRACT

Eprinomectin (EPM) is a veterinary drug currently licensed in many countries for the treatment of endo- and ecto-parasites in cattle. Despite the notable evidence for its high toxicity to the terrestrial and aquatic environment ecosystems, its environmental behavior and fate are currently unknown. In the present research, the dissipation of EPM was studied in three soils and in cattle manure by using the OECD 307 guideline and the recently developed European Medicines Agency (EMA/CVMP/ERA/430327) guideline, respectively. The procedure presented by the FOrum for Co-ordination of pesticide models and their USe (FOCUS) was adopted for estimating the EPM degradation kinetics in soil and cattle manure. The EPM dissipation in soil was best described by the SFO (Simple First Order) and the HS (Hockey Stick) models, under aerobic and anaerobic conditions, respectively. The EPM dissipation in cattle manure was best described by the FOMC (First Order Multi Compartment) model. The Dissipation Time for the 50% of the initial EPM mass (DT_{50}) range was 38–53 days under aerobic and 691–1491 days under anaerobic conditions. In addition, the DT_{50} for EPM in cattle manure was 333 days. Therefore, EPM could be characterized as moderately to highly persistent to dissipation in soil, which depends on soil type, its oxygen content (aerobic or anaerobic conditions in soil) and the microbial activity. Moreover, the EPM resists dissipation in cattle manure, resulting to a high load in soil after manure application in agricultural land (or direct defecation in grassland). Consequently, the high possibility for EPM accumulation in soil and cattle manure should be considered when assessing the environmental risk of the drug.

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1. Introduction

Maintaining an acceptable level of animal performance, under the current food production system, relies considerably on the use of veterinary drugs such as avermectins, since endo- and ecto-parasites impair livestock health and welfare (Merck, 1996; Omura, 2008; Sutherland and Leathwick, 2010). Eprinomectin (EPM) and the avermectins (AVMs) e.g. ivermectin, abamectin, emamectin, and doramectin, are members of the macrocyclic lactone (ML) family. The drugs are extensively used as parasiticides in animal husbandry, agriculture, aquaculture and pets treatment (Kovecses and Marcogliese, 2005; Lumaret et al., 2012; Omura, 2008) as well as in human medicine (Campbell, 1989; Danaher et al., 2006; Omura, 2008; WHO, 2010). The MLs have a similar structure and physicochemical properties. Their mode of action against the parasites is based on their interaction with the receptor channels for inhibitory neurotransmitters (Danaher et al., 2006). The high effectiveness of MLs raises concerns about their consequences on the non-target species (Lumaret et al., 2012; Merck, 1996; Sanderson et al., 2007; Williamson, 2005) and the resulting damage in the ecosystem functioning e.g. altering the aquatic and terrestrial species richness, food webs and nutrient cycling. The extensive use of avermectins might also lead to parasites resistance, a situation which is considered a global health and agricultural issue (Anziani et al., 2004; Edmonds et al., 2010; Ghosh et al., 2012; Lyndal-Murphy et al., 2009; Sutherland and Leathwick, 2010). Lumaret et al. (2012) published a quite detailed review on the toxicity and effects of MLs in the aquatic and terrestrial environment. This work demonstrated: 1) that MLs are substances of high concern particularly with larval instars and invertebrates, 2) that research so far focuses on ivermectin and to a lesser extent on abamectin, doramectin and moxidectin while 3) information on compounds such as EPM, emamectin and selamectin is scarce. Moreover, the research during the last few years mainly about the effects of ivermectin on ecosystem

Abbreviations: AVMs, avermectins; DT_{50}, Dissipation Time for the 50% of the initial EPM mass in soil or manure; DT_{90}, Dissipation Time for the 90% of the initial EPM mass in soil or manure; EMA/CVMP, European Medicines Agency/Committee for Medicinal Products of Veterinary Use; EPM, eprinomectin; ERA, Environmental Risk Assessment; FOCUS, FOrum for Co-ordination of pesticide models and their USe; Koc, organic carbon normalized K_d^{ads}; K_d^{ads}, adsorption distribution coefficient; K_d^{des}, desorption distribution coefficient; MLs, macrocyclic lactones; NOEC, NO Effect Concentration; OECD, Organization for Economic Co-operation and Development; SFO, Simple First Order kinetics model; HS, Hockey Stick model; FOMC, First Order Multi Compartment or Gustafson–Holden model; VICH, International Cooperation on Harmonization of technical requirements for registration of Veterinary medicinal products; w.w., wet weight; d.w., dry weight.

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functioning, using mesocosms studies (within the context of the EMA/VICH guidelines for ERA), revealed that the risk of using the AVMs as parasiticides is unacceptable (Jensen and Scott-Fordsmand, 2012; Liebig et al., 2010; Sanderson et al., 2007).

There is evidence that AVMs dissipate within a few weeks in case they remain in the soil surface and expose to ambient UV light (Halley et al., 1993; Merck, 1996; Pfizer, 1996). Opposing to the rapid AVMs elimination, is the recently published work for ivermectin and abamectin dissipation in soil (Krogh et al., 2009; Mougin et al., 2003), feces (Celestina et al., 2010; Pope, 2009) and sediments (Prasse et al., 2009), where DT_{50} values vary from a few weeks to a few years, depending mostly on the oxygen content and the presence and activity of microorganisms. According to these DT_{50} values, avermectins are classified as moderately to highly resistant to dissipation in the environment and as a result there is the threat of accumulation in the environment with time. Despite the high significance for the fate of avermectins, currently there are no data for the dissipation of MLs in the manure. Also opposing to the argument of rapid elimination are the findings of Boxall et al. (2006) and Xie et al. (2011). In the first study, avermectins (ivermectin and doramectin) were detected in sediments in a concentration range of 2.7–4.9 μg/kg (ppb) in the U.K., while in the second study avermectins (abamectin, doramectin and ivermectin) were found in much higher than expected concentrations (range: 9.3–12806 μg/kg) in agricultural fields with vegetables and in soil under animal husbandry facilities in China. Unfortunately, these are probably the only published studies so far to report avermectin detection in the environment.

The EPM (Fig. 1) was synthesized after modifying the abamectin chemical structure. The EPM physicochemical properties that influence its environmental behavior are presented in Table 1. The drug was designed, synthesized and selected among many other avermectin compounds to be highly efficient against a number of cattle endo- and ecto-parasites. Another major advantage of the drug, compared to other avermectins, is its low milk/blood distribution constant (Alvinerie et al., 1999). This is of major importance to the cattle industry because no withdrawal period is required and the milk could be consumed during and after the treatment with EPM. The EPM is excreted mainly through feces as non-metabolized drug (Merck, 1996). The drug could reach the soil directly from grazing livestock and indirectly through application of manure as a fertilizer in agricultural land (Boxall et al., 2006; Kummerer, 2008; Merck, 1996). The information about the ecotoxicity and fate of EPM is limited. In addition, appropriate analytical methods for EPM quantification in soil and cattle manure were recently developed and appropriately validated (Danaher et al., 2012; Litskas et al., 2010). According to Merck (1996) EPM could be a very serious threat to the aquatic Cladocera and the dung insects, at ppb (μg/L or μg/kg) level. The drug could also be toxic to earthworms (Halley et al., 2005), plants (e.g. germination, root elongation), fish, birds and mammals (Merck, 1996) although in relatively higher concentrations compared to those threatening dung insects and plankton. Lumaret et al. (2005) found that feces voided by cattle treated with eprinomectin were associated with high larval mortality during the first 12 days after treatment, with null emergence until day 7. The NOEC for *Neomyia cornicina* was estimated to be close to 7 ± 5 ng/g. Prousali (2009) presented a NOEC of 4 ng EPM/g cattle dung (w.w.) for the beetles *Aphodius sturmi* and *Euoniticellus fulvus*. On the contrary, the only published data for EPM degradation are the DT_{50} value of 64 days in soil, under aerobic conditions, and the finding that the drug was persistent to dissipation in cattle dung which was placed in the field (Merck, 1996).

Table 1
Physicochemical parameters of EPM.
Adopted by Merck (1996).

Parameter	Value
Density (g/cm^3)	1.23 ± 0.04
Water solubility (mg/L); pH 7.3	3.5 ± 0.2
Solubility in organic solvents	Freely soluble in polar organic solvents
Vapor pressure (Pascal); 22.5 °C	5.33×10^{-4}
Log(n-octanol/buffer partition coefficient); pH 6.8	5.4 ± 0.3
Hydrolysis (DT_{50}); aqueous buffer 25 °C	pH 4: 622 days pH 7: 2026 days pH 9: 414 days
Dissociation constant (pKa)	No pKa between pH 3–10
Melting point (°C); differential scanning calorimetry (DSC)	163–166

Therefore, it is important to assess the dissipation of EPM in soil and cattle manure after applying the OECD (2002) protocol 307 and the recently published guideline EMA/CVMP/ERA/430327 (EMA, 2009). The OECD (2002) guideline 307 presents a method designed for evaluating aerobic and anaerobic transformations of a chemical in soil. This protocol is repeatedly used for the estimation of the DT_{50} of pesticides while its use for veterinary medicines is currently limited. The EMA (2009) guideline on determining the fate of veterinary medicinal products in manure, in support of the CVMP/VICH guidelines (EMA, 2008), is the only existing guidance document attempting to standardize the methodology for dissipation studies in the manure of housed animals.

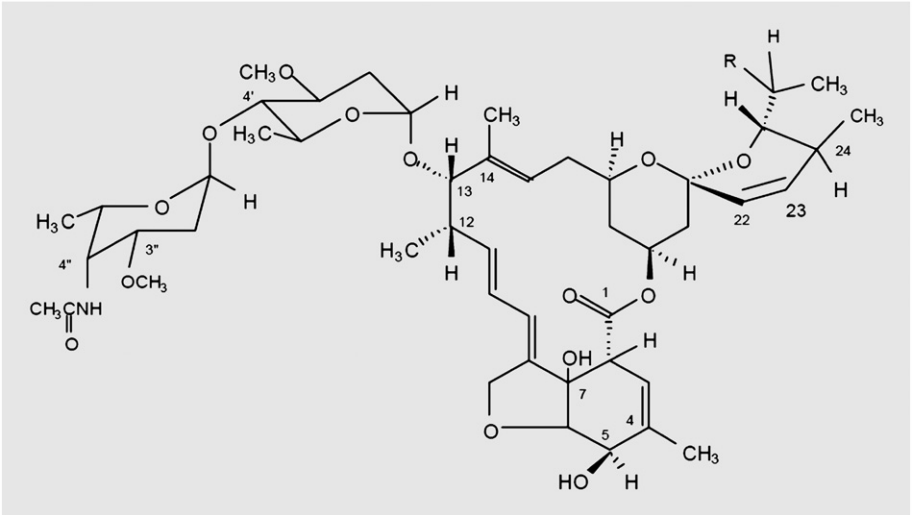

Fig. 1. EPM molecular structure. B1a component: R = C_2H_5; molecular weight = 914 and B1b component: R = CH_3; mol. weight = 900.

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