# Impact of using biocides on the stability of antibiotics in drinking water for pigs, poultry and rabbits

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**ABSTRACT**

Drinking water is an useful vector for the collective treatment of animals. This drinking water is generally disinfected with biocides prior to administration to animals to ensure its sanitary quality. In the absence of European requirements regarding the content of marketing authorisation dossiers on the compatibility of veterinary medicinal products with disinfectant biocides in drinking water, it proved necessary to assess the risk of potency loss for antibiotics administered by this route.

The general objective of the CABALE project (EcoAntibio 2017 plan) was to consolidate knowledge on the stability of antibiotics in the presence of biocides for the pig, poultry and rabbit sectors. This study aimed to assess the stability of six antibiotic active substances found in various veterinary products in drinking water, with low ("soft") or high ("hard") mineral content, in the presence of a biocide (sodium hypochlorite or hydrogen peroxide), in laboratory and in field water. Using standard laboratory water, antibiotic stability was assayed, on the one hand, in a situation equivalent to the storage of the concentrated stock solution of antibiotics for 24 h and, on the other hand, in a situation equivalent to the injection of the stock solution in the drinking system for 6 h. Liquid chromatography-UV detection analyses of the studied water samples demonstrated that the disinfectant biocides affected the stability of certain active substances. For the 10 veterinary medicinal products studied, treating the water with 50 ppm hydrogen peroxide affected the stability of only one active substance, amoxicillin. However, treating the water with sodium hypochlorite (0.5 ppm active chlorine) had a significant effect on the stability of seven veterinary medicinal products, especially in "hard" water (pH = 8; hardness 35°f, i.e. 350 mg/L). The second part of this study focused on a water directly collected in the field on a farm. The results using real farm water demonstrated that the stability of veterinary product solutions is multifactorial in nature. The multiplicity of factors affecting the use of biocides in drinking water must be taken into account to optimise the efficacy of antibiotic treatments administered orally in drinking water and to prevent the risk of antimicrobial resistance developing. Recommendations were issued and proposals were also made at European level to improve the recommendations in the EMEA/CVMP/540/03-Rev1 guideline on assessing the stability of antibiotics to be administered in drinking water.

**INTRODUCTION**

The bacteriological and physico-chemical sanitary quality of drinking water on farms must be controlled to protect the health of animals and of consumers of foodstuffs derived from farm animals [2]. Thus, drinking water is generally disinfected using biocides to ensure its sanitary quality.

Drinking water is increasingly being used as a vector for the collective treatment of animals [3]. This type of medication, which may require the use of metering pumps, is now very widespread in various livestock sectors, because it facilitates good compliance with therapeutic durations and weight-based dosages and provides a rapid and flexible method of administration.

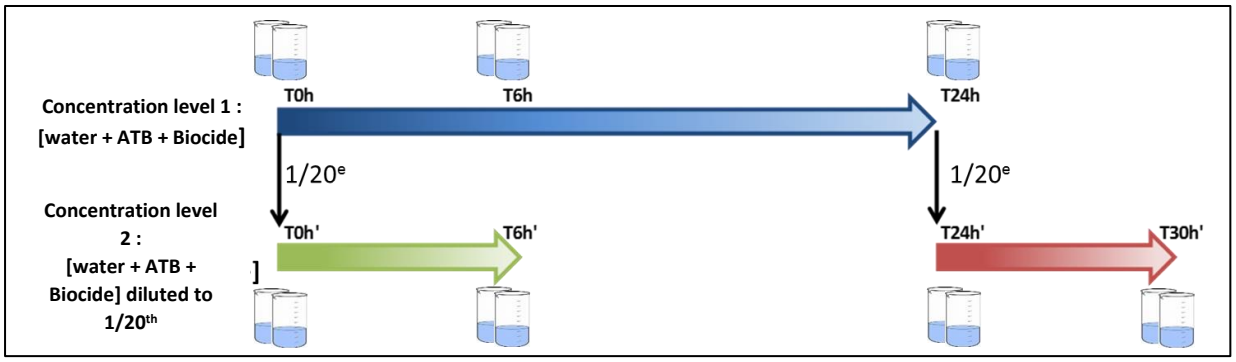


**Figure 1**: Study design for concentration levels 1 and 2 and studied time points

However, the simultaneous and concomitant presence of disinfectant biocides and antibiotics in drinking water raises the question of the biocides' impact on the stability of the antibiotics: is there a possible risk of antibiotics administered via drinking water losing their potency? The absence of requirements in the European guidelines regarding the content of marketing authorisation (MA) dossiers on the compatibility of veterinary medicinal products with disinfectant biocides in drinking water makes it necessary to provide some answers on this topic to prevent possible risks of therapeutic failure and the risk of selection for resistant bacterial strains.

In France, some initial answers regarding the pig sector were provided during a recent exploratory study entitled "Antibi'eau" financed by France AgriMer [6]. This study showed potency loss of more than 10% for amoxicillin and tylosin in the presence of hydrogen peroxide in a commercial spring water.

As part of the EcoAntibio 2017 plan, the "CABALE" study primarily aimed to determine the impact on the stability of antibiotic treatments of using biocides to disinfect drinking water for pigs, poultry and rabbits.

## MATERIALS AND METHODS

The study on the stability of antibiotics in the presence of biocides in drinking water was conducted in two parts. The first part of the study assessed the stability of antibiotics in the presence of biocides in "standard" waters according to the EMEA/CVMP/540/03 Rev.1 guideline [5]. The second part of the study consisted in assessing the stability of a selection of antibiotic-biocide pairs in a "field" water collected directly from a poultry farm.

### Part 1: Assays in standard laboratory water

The tested antibiotics were chosen based on sales volumes from 2015 and their use in drinking water in at least two of the three selected sectors [7] or, where applicable, according to their importance for veterinary medicine in the three represented sectors. The selected active substances were doxycycline, amoxicillin, sulfadiazine and sulfadimethoxine combined with trimethoprim, tiamulin and colistin. For each active substance, two veterinary products (VP 1 and VP 2) were tested, with the exception of sulfadiazine and sulfadimethoxine for which only one VP was tested. The VPs were chosen with the aim of studying a wide variety of formulations (liquid, powder) and excipients and ensuring proper representation of the various MA holders concerned and the studied livestock sectors.

Two biocides were chosen based on standard farming practices in France, i.e. 50 ppm hydrogen peroxide ($H_2O_2$) stabilised with orthophosphoric acid, and sodium hypochlorite (NaClO) with 0.5 ppm active chlorine.

The study of antibiotic stability in the presence of biocides was undertaken with two types of standard water, taking into account criteria specific to water quality, as defined in the position paper and guideline on the administration of veterinary medicinal products via drinking water [4, 5]; these waters were able to cover the wide variety of water quality classes that can be used on farms: i) soft water (pH = 6; 60 mg $CaCO_3$, equivalent to 6°f), ii) hard water (pH = 8; 350 mg $CaCO_3$, equivalent to 35°f).

Analytical methods based on liquid chromatography coupled with a UV detector (LC-UV) were optimised, validated over the concentration range of interest for each active ingredient, and then used for assays during the stability study, except for the assay for colistin for which the linearity and repeatability of the responses could not be verified.

Potency loss for active substances in veterinary products administered via drinking water containing

biocides was therefore assessed at two concentration levels, i.e. (**Figure 1**): i) At the concentration of the stock solution kept in a mixer for 24 h – Concentration level 1; ii) At the concentration of the treatment dosage defined in the summary of product characteristics (SPC), over a period of 6 h. This solution was obtained from a 1:20 dilution of the stock solution, simulating a metering pump adjusted to 5% – Concentration level 2.

The first concentration level (i.e. that found in a mixer) dealt with antibiotic stability over a period of 24 h, corresponding to the maximum period during which the stock solution can be kept in a mixer [4, 5] (**Figure 1**). An intermediate measurement was also taken after 6 h.

The second concentration level (i.e. that found in distribution pipes) simulated a diluted solution transported in pipes to drinkers and was used to monitor the stability of the active substance for 6 h. This interval was arbitrarily defined as being the maximum period during which the treatment solution can flow through pipes. This diluted solution was obtained by a 1:20 dilution of the stock solution at time T0 and then at time T24h. The samples diluted at T0 and T24h were monitored for 6 h (intervals T6' and T30', **Figure 1**). These two intervals were defined as being representative of field conditions, especially when the concentrated drinking water, prepared 24 h prior, is diluted 1:20 for distribution in pipes at the nominal level of active substance set out in the SPC. This scenario represents a situation of assumed maximum degradation of the active substance.

For each of the study's target veterinary products, each of the concentration levels was studied in duplicate. In addition, stability studies for concentration levels 1 and 2 were also undertaken in duplicate with "control" samples, i.e. samples not containing any biocide (containing [water+veterinary product] only).

At each interval, the stability of the veterinary products was expressed as the percentage recovery of the average concentrations of active substance(s) contained in the samples with biocide compared with the average concentration in the samples without biocide (i.e. the control samples), and not compared with therapeutic doses defined in the MAs. An active substance having lost more than 10% of its concentration compared with the control without biocide at a given interval and having reached a p-value threshold below 0.05 (*t*-test) was considered as being unstable. This threshold value of 10% loss was approved by consensus of the project's steering committee and corresponds to the maximum acceptable limit in MA dossiers. Graph Pad® software (Prism v. 5.04) was used for these analyses.

The data were also statistically analysed to assess, using mixed models, the effects of the biocide, water hardness and time on concentrations of active substances for each veterinary product, in a concentrated solution and a diluted solution.

**Part 2: Assays in field water**

In Part 2 of the study, a "field" water was used for antibiotic stability testing, but with a smaller number of veterinary products, due to time constraints associated with the project. The objective of this phase was to assess the impact of iron and manganese in drinking water on farms on the stability of antibiotics in the presence of hydrogen peroxide (50 ppm).

The type of water chosen for Part 2 was a surface well water, with high concentrations of iron and manganese, to assess the impact of these two elements on the stability of veterinary products. The concentrations of iron and manganese were at least twice as high as the regulatory limits for water intended for human consumption [1]: total iron ≥ 2 x 200 µg/L, and manganese ≥ 2 x 50 µg/L. The water sample had the following properties: a pH of 6.0, hardness of 90 mg/L (9.0°f), and iron and manganese concentrations of 536 µg/L and 117 µg/L, respectively. Three active substances were studied in Part 2: amoxicillin (VP 2), widely used in the pig sector; tiamulin (VP 1), commonly used in the rabbit sector; and doxycycline (VP 2), used in the poultry sector, among others.

The 30 h stability testing methodology, the assay methods and the data analysis used in Part 1 were replicated (**Figure 1**).

**Table 1**: Stability (%) or percentage recovery of the average concentrations of active substance in the samples after treatment compared with the average concentration in the control samples

| | | | Doxycyclin | | Amoxicillin | | Sulfonamides (Sulfa + TMP) | | Tiamulin | | Colistin (E2 + E1) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | VP 1 | VP 2 | VP 1 | VP 2 | VP 1 | VP 2 | VP 1 | VP 2 | VP 1 | VP 2 |
| $H_2O_2$ | Soft water | T0 | 97,1 | 94,9 | 97,6 | 103,1 | 97,1 | **93,0*** | 101,9 | 106,0 | 98,8 | 98,7 |
| | | T6 | 100,2 | 102,9 | 99,1 | **72,4*** | ND | 106,1 | 101,6 | 98,7 | 97,7 | 100,6 |
| | | T24 | 96,7 | 103,7 | 101,2 | **67,2*** | 97,6 | 85,6 | 100,6 | 99,1 | 101,1 | 100,4 |
| | | T0' | 95,0 | 105,9 | 97,4 | 99,6 | 100,9 | 99,3 | 100,9 | 102,0 | 95,3 | 98,8 |
| | | T6' | 94,8 | 99,5 | 96,5 | **51,5*** | 99,3 | 90,7 | 100,1 | 107,0 | 97,1 | **98,5*** |
| | | T24' | 97,0 | 97,3 | 96,9 | **66,7*** | 100,4 | 99,8 | 99,1 | 98,0 | 101,3 | 100,4 |
| | | T30' | **97,2*** | 97,2 | 93,6 | **42,7*** | 99,6 | 95,8 | 98,4 | 101,5 | 103,7 | 100,2 |
| | Hard water | T0 | 103,1 | 100,3 | 96,6 | 95,7 | 96,7 | 101,1 | 101,8 | 98,4 | 98,0 | 99,7 |
| | | T6 | 100,0 | 99,6 | 95,4 | **68,2*** | 98,2 | 101,3 | 101,4 | 100,3 | 99,9 | 100,6 |
| | | T24 | 101,7 | 101,5 | **88,0*** | **70,2*** | 100,3 | 99,7 | 101,5 | 99,2 | 100,6 | 99,7 |
| | | T0' | 99,5 | 100,7 | 99,1 | 94,8 | 92,5 | 97,0 | 96,3 | 100,5 | 100,4 | 99,6 |
| | | T6' | 99,3 | 98,7 | **66,1*** | **33,9*** | 100,2 | 101,5 | 93,6 | 101,3 | 100,3 | 98,6 |
| | | T24' | 98,7 | 99,7 | **88,2*** | **65,4*** | 98,9 | 97,6 | 99,0 | 107,9 | 100,3 | 99,7 |
| | | T30' | 104,0 | 99,6 | **61,4*** | **27,2*** | 100,3 | 98,6 | 100,0 | 101,5 | 100,9 | 99,5 |
| HOCl | Soft water | T0 | 98,6 | 96,3 | **95,3*** | 101,1 | 100,9 | 93,3 | 97,8 | 99,3 | 104,2 | 98,8 |
| | | T6 | 98,9 | 93,1 | 100,1 | 95,3 | 102,9 | 91,9 | 99,0 | 96,7 | 96,1 | 100,1 |
| | | T24 | 97,6 | 87,9 | 100,3 | **93,6*** | 101,8 | 100,3 | 100,2 | 98,0 | 98,8 | 99,1 |
| | | T0' | 96,0 | 95,5 | 94,7 | **98,6*** | 96,8 | 102,7 | 91,1 | **92,0*** | 87,8 | **74,9*** |
| | | T6' | 98,3 | **94,6*** | 95,2 | 98,6 | 98,0 | 84,8 | 97,0 | **91,7*** | **82,7*** | **73,3*** |
| | | T24' | **93,9*** | **94,6*** | 97,2 | 96,5 | 99,0 | 99,9 | 98,1 | **92,8*** | **81,5*** | **73,7*** |
| | | T30' | **95,5*** | **94,1*** | 101,1 | 97,4 | 96,7 | 96,9 | 95,7 | **93,8*** | **79,9*** | **73,5*** |
| | Hard water | T0 | 99,4 | 91,8 | 105,6 | 99,1 | 97,9 | 107,9 | 99,3 | 98,2 | 101,3 | **89,7*** |
| | | T6 | 99,1 | 97,0 | 101,7 | **98,3*** | 94,7 | 101,6 | 99,6 | 100,0 | 99,2 | **89,8*** |
| | | T24 | 99,6 | 98,0 | 104,3 | **103,2*** | 94,0 | 101,4 | 100,5 | 98,1 | ND | **89,7*** |
| | | T0' | **87,7*** | **86,5*** | 88,4 | 90,1 | 95,5 | 100,0 | **90,8*** | **63,4*** | **84,3*** | **24,3*** |
| | | T6' | **87,8*** | **83,6*** | **86,3*** | **87,5*** | 100,7 | 91,4 | **91,9*** | **63,2*** | **75,5*** | **29,6*** |
| | | T24' | **88,9*** | 85,9 | 91,9 | **91,1*** | 90,5 | 99,3 | 90,8 | **68,9*** | **65,5*** | **35,4*** |
| | | T30' | **88,5*** | 84,5 | **90,7*** | **89,8*** | 100,9 | 95,5 | **85,1*** | **70,2*** | **64,5*** | **33,6*** |

Assay < 90% | *** = Significant result** | ND = Non Determined

## RESULTS AND DISCUSSION

In general, for the 10 studied veterinary medicinal products (6 target active substances), treating the water with 50 ppm hydrogen peroxide only affected the stability of one active substance, amoxicillin (VPs 1 and 2), after 6 h in soft and hard water, whether the solution was concentrated or diluted. Average losses of 12% to 73% (corresponding respectively to 88% and 27% recovery) were observed between 6 and 30 h (**Table 1**).

However, treating the water with sodium hypochlorite (0.5 ppm active chlorine) was found to have a significant effect on the stability of seven VPs.

The VPs that were prepared in hard water and diluted (i.e. amoxicillin, doxycycline, tiamulin and colistin) were significantly sensitive to the presence of sodium hypochlorite during the 30 h of sample monitoring (between 24% and 90% stability), whereas colistin (VPs 1 and 2, between 73% and 88% stability) was also sensitive in diluted soft water (**Table 1**). One of the factors that may explain these results is the concentration of total chlorine, which was three times higher in the samples prepared in hard water (a relatively basic pH) than in those prepared in soft water, to obtain 0.5 ppm active chlorine. The pH often decreased after the veterinary products were added to the water, thus increasing the activity of the available chlorine in the sample.

Chlorine in hard water (pH of 8 and hardness of 350 mg/L (35°f)) therefore had a significant effect. In practice, obtaining 0.5 ppm active chlorine in hard water (pH 8, 350 mg/L (35°f)) before adding the medicinal product requires adding around three times more sodium hypochlorite than for soft water (pH 6, 60 mg/L (6°f)). Thus, the total chlorine content is three times higher in hard water than in soft water. Adding the doxycycline, amoxicillin, tiamulin and colistin veterinary products significantly decreased the pH of the "hard" water: less than pH 4 for doxycycline (except in the diluted solution of VP 2 where the pH was around 6.5), pH ranging from 6.1 (concentrated solution) to 7.8 (diluted solution) for amoxicillin, pH ranging from 3.8 (concentrated solution) to 7.0 (diluted solution) for tiamulin, and pH ranging from 6.4 (concentrated solution) to 7.8 (diluted solution) for colistin. At a pH of less than 6, the total chlorine (HOCl, ClO-, chloramines, organochlorines) in the solution occurs in the form of active chlorine (HOCl) and can therefore chemically interact with the active substance and affect its stability. Because the initial level of total chlorine is higher in prepared hard water solutions

than in soft water solutions, the active chlorine concentrations generated by adding medicinal products to this type of water are higher, exceeding 0.5 ppm. This appears to increase the potential action of chlorine on the stability of active substances. This study showed that the action of the medicinal products on the pH of the solutions was “formulation dependent”. However, two studied medicinal products containing sulfonamides did not cause any decrease in the pH of the prepared hard water. Furthermore, these two medicinal products did not undergo any significant loss of sulfonamide concentrations compared to the controls without biocide. The pH of a “test” solution containing the “field” treatment water and the veterinary medicinal product could be measured prior to the solution's preparation in a mixer to determine if chlorine can be used. Thus, in the event of a medicinal product that acidifies an initially hard solution (pH 8, 350 g/L (35°f)) treated with sodium hypochlorite 0.5 ppm, it is preferable to treat the water with hydrogen peroxide to disinfect it.

Moreover, on farms where the water contains high concentrations of iron and manganese, farmers preferentially use hydrogen peroxide because the active chlorine can be neutralised by these two elements (oxidation of iron and manganese by chlorine).

Chlorine in soft water did not seem to pose problems, except for colistin after injection in pipes. This was the only finding that differed from the conclusions of the Antibi'eau study, which had a different protocol [6]. In the Antibi’eau study, no colistin degradation was noted, even after 1 h of contact with chlorine in pipes [6]. The studied veterinary product, however, may have been different from those tested in CABALE, which demonstrated a pronounced “veterinary product dependent” effect (VP 2 was affected more than VP 1).

Regarding the two studied sulfonamide VPs, they proved to be stable regardless of the tested laboratory conditions (type of water, type of biocide, concentration of active substance).

Furthermore, the mixed-model analysis highlighted the potential effects of various parameters: time, dilution, hardness and veterinary product. It confirmed the significant effect of the disinfectant biocide on almost all of the solutions of veterinary products, whether concentrated or diluted (results not given). Only the concentrated solutions of sulfonamides and colistin, and one of the doxycycline veterinary products, did not seem affected by the presence of any disinfectant biocide in water.

The results obtained in Part 2, in “field” water, with water collected from a farm and having high iron and manganese levels, were generally consistent with those obtained in Part 1 with standard laboratory waters for amoxicillin and tiamulin (Table 2). Thus, high iron and manganese concentrations did not seem to affect the stability of the studied veterinary products.

However, the results obtained for doxycycline were contrasted between Parts 1 and 2 of the study. Stability was significantly affected by the presence of hydrogen peroxide in the field water tested (Part 2), whereas it had been preserved in a standard water (Part 1). However, these results cannot be rigorously compared with one another.

**Table 2**: Stability (%) or percentage recovery of the average concentrations of active substance in the veterinary products after treatment with hydrogen peroxide in soft water, in Part 1 (controlled laboratory conditions and Part 2 (field conditions) of the study – comparison of stability between the samples with and without biocide.

| | | | Doxycycline VP 2 | | Amoxicillin VP 2 | | Tiamulin VP 1 | |
|---|---|---|---|---|---|---|---|---|
| | | | Phase 1 | Phase 2 | Phase 1 | Phase 2 | Phase 1 | Phase 2 |
| $H_2O_2$ | Soft Water (phase 1) o Field water with Fe+Mn (phase 2) | T0 | 94,9 | 99,7 | 103,1 | 91,2 | 101,9 | 96,9 |
| | | T6 | 102,9 | 98,6 | **72,4*** | **73,9*** | 101,6 | 95,5 |
| | | T24 | 103,7 | **88,2*** | **67,2*** | **66,2*** | 100,6 | 100,5 |
| | | T0' | 105,9 | 99,2 | 99,6 | 98,5 | 100,9 | 91,7 |
| | | T6' | 99,5 | **68,7*** | **51,5*** | **85,9*** | 100,1 | 97,2 |
| | | T24' | 97,3 | **89,6*** | **66,7*** | **66,7*** | 99,1 | 92,0 |
| | | T30' | 97,2 | **73,6*** | **42,7*** | **51,9*** | 98,4 | 99,7 |

| | |
|---|---|
| Stability < 90% | *** = Significant results** |

No tangible conclusions can be drawn, because the sample of water did not have the same physico-chemical and bacteriological properties as the two other samples collected during Part 2. The water sampling site used at the time of the doxycycline study was strongly impacted by heavy precipitation over the previous days. A change in water quality caused by various climate events (hardness, pH, mineral composition, organic matter, etc.), instability at the intake point, an increase in water temperature or any other factor causing drinking water to be physico-chemically or biologically modified may therefore have an effect on the stability of the active substances, which were initially stable in standard laboratory or routine field conditions. The variability of "field" waters cannot be controlled, as it can in laboratory conditions (Part 1). Therefore, Part 2 of this study also highlighted the multifactorial nature of the stability of VP solutions in field conditions.

**RECOMMENDATIONS**

In light of this project's results and its scope, the following recommendations can be issued:

- Whenever possible, the pipes should be opened at the end of the line to supply the medicated water to the animals in real time;
- It is also advisable to prepare a quantity of medicated stock solution intended to be consumed in full during the day (at most), to prevent the active substances from stagnating in pipes for too long and reduce the risk of degradation by chlorine, in particular; as a precautionary measure, whenever possible, it may be preferable to prepare and administer the medicated solution on a half-day basis;
- Farmers should have good knowledge of how to properly use and regularly monitor the metering pump and should be familiar with how it works; they should also be aware of the quality of the water administered to the animals (in particular its physico-chemical parameters);
- Veterinarians should also be aware of factors influencing the stability of veterinary medicinal products in drinking water and should be able to assess the quality of a system for distributing medicinal products via drinking water to take it into account in their prescriptions; among other things, the pH of the chlorinated water could be verified before and after adding the medicinal product, to recommend the most appropriate biocide;
- Because the stability of an active substance can vary depending on the formulation of the veterinary product, it would be useful for MA holders to undertake additional studies on the stability of their veterinary products in various types of water containing various biocides to issue recommendations for use and indicate points requiring attention when preparing medicated solutions on farms.

Given that only two veterinary products per active substance were studied during this project, the results obtained here cannot be extrapolated to all veterinary products containing the same active substance in their formulation. It is therefore not possible to issue recommendations for use for all veterinary products prepared in water in the presence of a particular biocide.

**CONCLUSION**

Supplementing the results of the Antibi'eau project, this CABALE study provided new data and confirmed the impact of disinfectant biocides on the stability of certain antibiotics in the drinking water of pigs, poultry and rabbits. This project's conclusions only apply to the 10 studied veterinary products and therefore cannot be extrapolated to all veterinary products having the same active substance in their formulation.
Regarding veterinary products undergoing degradation due to a disinfectant biocide in water, it is of interest to study the fate of the active substances and identify their transformation products to ultimately assess their toxicity.

The stability analyses in a field water containing high concentrations of iron and manganese and treated with hydrogen peroxide confirmed the results obtained during the tests with amoxicillin and tiamulin in standard waters prepared in a laboratory. No conclusions could be drawn for doxycycline due to the variability of the results obtained, which was likely due to the impact of the season and climate on the quality of the field water assayed.
All of these findings demonstrated the multifactorial nature of a real-life, complex field situation, which should be taken into account to optimise the efficacy of antibiotic treatments in drinking water and avoid the risk of under-dosing, which can lead to the development of antimicrobial resistance.

Recommendations for good practices were issued and will be disseminated to farmers and veterinarians via various channels.

This project's results also made it possible to submit proposals to improve the European recommendations in the EMEA/CVMP/540/03-Rev1 guideline on assessing the stability of antibiotics to be administered in drinking water. An agreement in principle was given by the Quality Working Party to start by adopting two texts called Questions/Answers for subsequent amendments.

Moreover, as part of the new European regulations on veterinary medicinal products, appropriate measures should be defined to ensure the effective and safe use of veterinary medicinal products authorised and prescribed for oral administration. The work undertaken during this project will enable the French authorities to report these recommendations to European authorities.

**ACKNOWLEDGEMENTS**

**Funding:** EcoAntibio 2017 plan

The authors thank the technical staff of the ITAVI and IFIP who took the water samples on farms.

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