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Withdrawal periods after treatment of pigs with oxytetracycline in- and outside the European Union

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ABSTRACT

Withdrawal periods are used to avoid animals being delivered to slaughter before the concentration of the antimicrobial has declined to values below the maximum residue limit (MRL). This paper characterises the withdrawal periods in force for oxytetracycline 100 mg/ml for intramuscular use in pigs. We investigated the variation in duration of the withdrawal period between 68 oxytetracycline products from 29 countries in- and outside the European Union. More specifically, we tested whether there is a regional difference, a difference between major and minor pig meat exporting countries, whether the product is long-acting or not, and whether year of market authorisation correlated with the withdrawal period. The results showed a large variation in duration of the withdrawal periods, ranging from 5 to 40 days. Variation was observed both between and within countries. Moreover, major exporting countries were associated with a longer withdrawal period than minor exporting countries ($P = 0.00099$). There were no regional differences, and the year of market authorisation had no impact, but long-acting products had a shorter withdrawal period than short-acting products ($P = 0.048$). The variation in withdrawal periods observed questions the utility of using compliance with the withdrawal period as a means of assessing whether the meat is safe for consumption. This is particularly relevant when a pig producer unintentionally delivers pigs for slaughter before the withdrawal period has expired and, aware of this, informs the abattoir. The findings call for further harmonisation in determining the withdrawal periods for all veterinary medicinal products (VMP). Until this happens, if animals are prematurely sent to slaughter, we suggest that the concentration of the VMP at the time of slaughter is calculated and compared with the MRL to determine meat safety.

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1. Introduction

The duration of the withdrawal period is listed in the specific product summary of all legal, veterinary medicinal products (VMP) used in production animals. The withdrawal period is set nationally or internationally and is based on the maximum residue limit (MRL), which is the maximum allowed concentration of a given residue in a carcase or a food product due to the treatment of an animal using a certain VMP (European Medicines Agency, 2023). The MRL is a legally binding food safety standard, which is set for a large geographical area, e.g., the European Union (EU), the USA, or The Russian Custom's Union (Léger et al., 2019). In the EU, the calculations for a given pharmacologically active substance follow the guidelines developed by the European Medicines Agency (European Medicines Agency, 2022a). The MRL is derived from the acceptable daily intake value over a lifetime (ADI), wherein no pharmacological effect is expected in humans due to the residue in food products (European Medicines Agency, 2012). A separate toxicological and microbiological ADI is derived based on the ingestible amount without adverse toxic side effects or antimicrobial activity, depending on the desired pharmacological effect (European Medicines Agency, 2012). The ADI used in the MRL calculation is generally the lowest of the two ADIs (EU Commission, 2018). For most legal antimicrobials, toxicological aspects are not relevant as the product has been accepted for use in humans. Therefore, the microbiological ADI is used, corresponding to a maximum daily ingested amount of residue per kilogram bodyweight over a lifetime with no observed adverse effect to either the colonisation barrier or increase in the population of resistant bacteria (European Medicines Agency, 2019).

Tetracyclines are the second most used drug class in European livestock production, following penicillins (European Medicines Agency, 2021). It is mostly used orally in weaner pigs to treat post-weaning diarrhoea (Moura et al., 2023). Oxytetracycline is a tetracycline that can be used for intramuscular and intravenous injection or oral treatment and is often used to treat respiratory diseases and *Mycoplasma*-induced lameness in finishers and sows (Papich, 2021).

In this paper, we shall consider a case involving the accidental delivery of pigs for slaughter before the end of the withdrawal period following antimicrobial (AM) treatment and the actions taken by the abattoir and the competent authority. In this situation, the abattoir must trace the individual pig(s) or carcase(s). If this is not possible, the abattoir may be forced to condemn or withdraw all products from the lot or the entire day, regardless of the actual residue level in the animal product. Consequently, the pig meat becomes food waste and the resources (e.g., feed, land, and labour) used for producing the pig meat are lost. In addition, the pig producer may receive a fine due to incorrect handling of the food chain information (FCI) (Alban et al., 2023).

Official testing of live animals, carcases or meat thereof based on a suspicion of residue of a non-illegal VMP was possible from 1996 (EU Council, 1996). This allowed the competent authority under defined circumstances to test whether the live animal(s) for slaughter or the carcase(s) or the meat thereof, was complying with the MRL and, therefore, considered as safe for human consumption. This practice was abolished in 2019 (EU Commission, 2019a).

The question is whether compliance with the withdrawal period can be used to judge compliance with the MRL. Working group 1 (WG1) within the RIBMINS COST Action network investigated this for oxytetracycline. For more information about RIBMINS and the activity on AM residues, please see https://ribmins.com/survey-on-residues-of-antimicrobials-in-pigs/. In this paper, we describe the variation in the duration of the withdrawal period for oxytetracycline, between and within countries in and outside the EU and possible determinants thereof.

2. Material and methods

2.1. Data collection

We focused on oxytetracycline (ATC: QJ01AA06) because of its acceptance and wide availability worldwide. Oxytetracyclines are found in both a short- and a long-acting formulation depending on the suspension (Papich & Riviere, 2018, pp. 867–868). The half-life has been reported to be in the range of 6 h–11 h for the simple formulations and around 37 h for the long-acting formulations (Papich & Riviere, 2018, pp. 867–868; Purdue Research Foundation, 1996). Moreover, the ADI of oxytetracycline is 180 μg for a person weighing 60 kg (EMEA, 1995).

We restricted the data collection to oxytetracycline products with a 100 mg/ml concentration, corresponding to 10%, and authorised for intramuscular injection in pigs. Other concentrations of oxytetracycline, along with products registered for different routes of administration than intramuscularly or registered strictly for other animal species, were excluded from the search to limit the causes of variation.

Between May and June 2023, the RIBMINS WG1 collected information about all oxytetracycline products fulfilling the inclusion criteria through their network. The countries of interest covered Europe as well as Australia, New Zealand and the USA. The focus was on the recommended dosage, whether it was long-acting or not, duration of the withdrawal period, marketing name, authorisation holder and year of first authorisation (when available) in the respective countries. The oxytetracycline products were found by searching the internet, focusing on major VMP databases of specific product summaries in each country.

The collected data were cleaned by the following procedure:

- Two oxytetracycline products were removed because they were licensed for being administered by routes other than intramuscular.
- 19 oxytetracycline products were removed because they contained concentrations greater than 100 mg/ml.

In some cases, the oxytetracycline product had multiple withdrawal periods depending on whether a 24-h or 48-h dosage regime was administered. The 24-h dosage regime required a daily injection over multiple days, whereas the 48-h dosage regime only required a single injection. Therefore, in each case of multiple dosage regimes, the withdrawal period of the 24-h dosage regime was chosen for simplicity and its similarity in dosage to the products with only a single dosage regime. When converting the dosage from a range to a single value for analysis, the highest dosage was chosen.

Furthermore, five new variables were added during the data cleaning and editing. The first was whether the product was long-acting or not. The second and third was correcting the withdrawal periods and dosages according to the above, and the fourth was the region of Europe, where the countries were divided into Northern, Southern, Western, Central- and Eastern countries as well as countries outside Europe (EU Publications Office, 2023). The fifth variable was whether the country could be considered a major or minor exporting country, based upon export volume and proportion of pig meat exported (Table 1). In the present analysis, a large exporter would have an export volume above 250,000 tons, representing >25% of the produced pig meat, and all other countries were considered as minor exporters (Alban et al., 2023).

2.2. Methods

The collected data describing the oxytetracycline products were imported to and analysed in R (R Core Team, 2023) using the openxlsx, tidyverse, ggrepel, flextable and bibtex packages (Francois & Hernangómez, 2023; Gohel & Skintzos, 2023; Schauberger & Walker, 2023; Slowikowski, 2023; Wickham et al., 2019). Initially, the focus was on identifying each participating country's minimum, median, and maximum withdrawal periods. Next, the difference between the maximum and minimum was plotted against the maximum withdrawal

Table 1
Importance of pig meat export for each of 29 countries, from where information about duration of the withdrawal period related to intra-muscular treatment with oxytetracycline was collected. Adapted from Alban et al. (2023).

		Proportion of pig meat exported	
		Major (≥25%)	Minor (<25%)
Volume of pig meat production in 1000 tonnes	Major (≥250)	Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Poland, Spain, The Netherlands, USA	
	Minor (<250)	Bosnia and Herzegovina, Estonia, Latvia	Australia, Croatia, Cyprus, Finland, Greece, New Zealand, North Macedonia, Norway, Portugal, Romania, Sweden, Switzerland, UK, Ukraine, Serbia and Montenegro

period in each country. Finally, the plot was used to formulate four hypotheses to further investigate potential determinants for variation in the withdrawal periods:

Hypothesis 1. Major exporting countries have a longer withdrawal period than minor exporting countries.

Hypothesis 2. Northern and Western European countries have a longer withdrawal period than the rest of the countries.

Hypothesis 3. The year of the first market authorisation is correlated to the length of the withdrawal period, so older products have a longer withdrawal period than newer products.

Hypothesis 4. The duration of the withdrawal period is longer if the product is a long-acting formulation.

The significance of the first and fourth hypotheses were tested using a Wilcoxon ranked sum test with continuity correction. The second hypothesis was tested using a variance analysis and the third with a linear model's coefficient of determination (R^2).

3. Results

The results are based on 68 products from 29 countries in- and outside the EU. A total of 11 countries were considered as major exporters of pig meat, whereas 18 were considered d as minor exporters (Table 1). The withdrawal period ranged between 5 and 40 days with a median of 14 days (Table 2). There was a clear correlation between the maximum withdrawal period and the maximum difference between the minimum and maximum withdrawal period in the same country (Fig. 1).

The first hypothesis evaluated whether there was a correlation between a country's exporting status with respect to pig meat (major/minor) and the length of the withdrawal period. The analysis showed a marked difference in the withdrawal period between the 11 major exporters (covering 33 oxytetracycline products) and the 18 minor exporting countries (covering 35 similar products) (Fig. 2), suggesting that major exporting countries had a longer withdrawal period, verified by a Wilcoxon ranked sum test with continuity correction ($P = 0.00099$). The major exporters had a wider range in withdrawal periods with a minimum of 7 days and a maximum of 40 days compared to 5 and 30 days for the minor exporters. While the median withdrawal periods were 15 and 12 days respectively, the interquartile range (Q3-Q1) was 9 days for the major exporters and days for the minor exporters. Thus, the major exporters exhibited a greater variation in withdrawal periods, whereas the minor exporters had a more concentrated distribution.

The second hypothesis dealing with regional differences was tested with an ANOVA analysis with a test statistic of $F = 0.977$ ($P = 0.427$), indicating no difference in the length of the withdrawal period between Northern and Western Europe and the remaining regions (Fig. S1).

Table 2
Summary of the data analysed, detailing the number of products and the minimum, median, and maximum withdrawal period of the 68 oxytetracycline products, each with a concentration of 100 mg/ml, registered for intramuscular use in pigs in 29 countries. Countries marked with * indicate that long-acting oxytetracycline products were on the market.

Country	No. of products	Withdrawal period (days)		
		Minimum	Median	Maximum
Australia	1	10	10.0	10
Austria	3	8	14.0	21
Belgium*	1	11	11.0	11
Bosnia and Herzegovina	3	8	12.0	14
Croatia	1	10	10.0	10
Cyprus*	2	7	7.5	8
Denmark	2	14	22.0	30
Estonia	2	8	11.0	14
Finland*	1	14	14.0	14
France	3	14	14.0	14
Germany	2	14	17.5	21
Greece*	2	5	6.0	7
Ireland	4	13	21.0	28
Italy	4	8	13.5	40
Latvia	2	8	18.0	28
Netherlands*	7	15	21.0	35
New Zealand	1	10	10.0	10
North Macedonia	2	12	20.0	28
Norway	1	30	30.0	30
Poland	2	7	10.5	14
Portugal*	3	10	14.0	24
Romania*	5	7	14.0	28
Serbia	2	14	14.0	14
Spain	2	14	19.0	24
Sweden	1	8	8.0	8
Switzerland	1	8	8.0	8
Ukraine	1	12	12.0	12
United Kingdom	4	11	12.5	14
USA	3	20	22.0	26
Total: 29	Total: 68	Min.: 5	Median: 14	Max.: 40

The third hypothesis was tested with a linear model with a test statistic of $F = 1.53$ ($P = 0.22$, $R^2 = 0.034$), rejecting the hypothesis of an association of the length of the withdrawal period based on the year of first market authorisation (Fig. S2).

The fourth hypothesis evaluated whether the duration of the withdrawal period between short- and long-acting products differed. The analysis showed that long-acting products ($n = 7$) had a shorter withdrawal period than short-acting products ($n = 61$) (Fig. 3), verified by a Wilcoxon ranked sum test with continuity correction ($P = 0.048$). The short-acting products had a wider range in withdrawal periods with a minimum of 5 days and a maximum of 40 days compared to 7 and 35 days for the long-acting. While the median withdrawal periods were 14 and 10 days respectively, the interquartile range (Q3-Q1) was 9 days for the short-acting and 5.5 days for the long-acting. Thus, the short-acting exhibited a greater variation in withdrawal periods, whereas the long-acting had a more concentrated distribution partly due to fewer products. Additionally, Fig. S3 shows that there was a lack of association between the highest dosage recommended and the duration of the withdrawal period.

4. Discussion and perspectives

4.1. Discussion

Although information was acquired for about 68 oxytetracycline products, each with a concentration of 100 mg/ml and licensed for intramuscular use in pigs, the survey is probably not fully

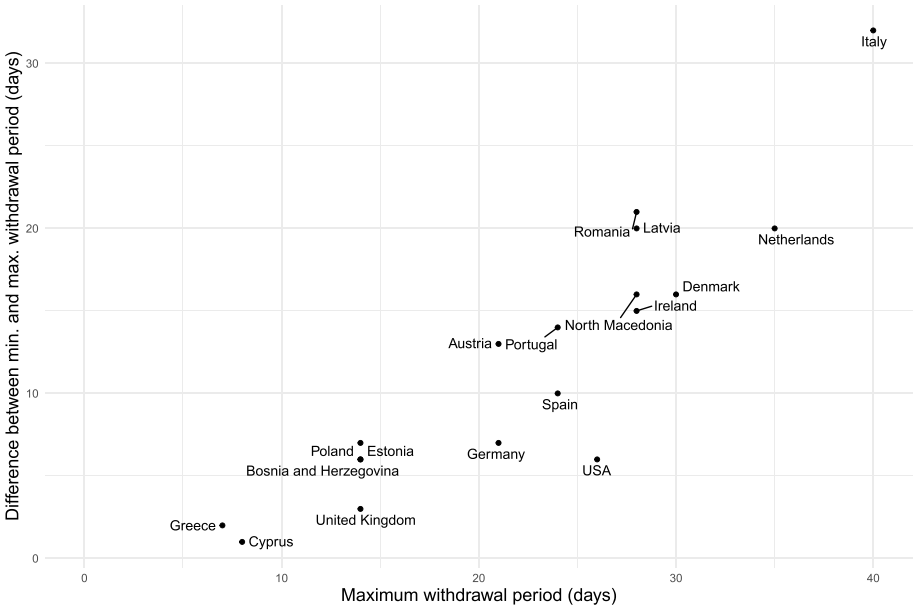

Fig. 1. The maximum withdrawal period plotted against the difference between the minimum and maximum withdrawal period for 18 countries in which multiple products are registered. The plot does not include countries with a single product or multiple products with identical withdrawal period such as Australia, Belgium, Croatia, Finland, France, New Zealand, Norway, Serbia, Sweden, Switzerland, and Ukraine.

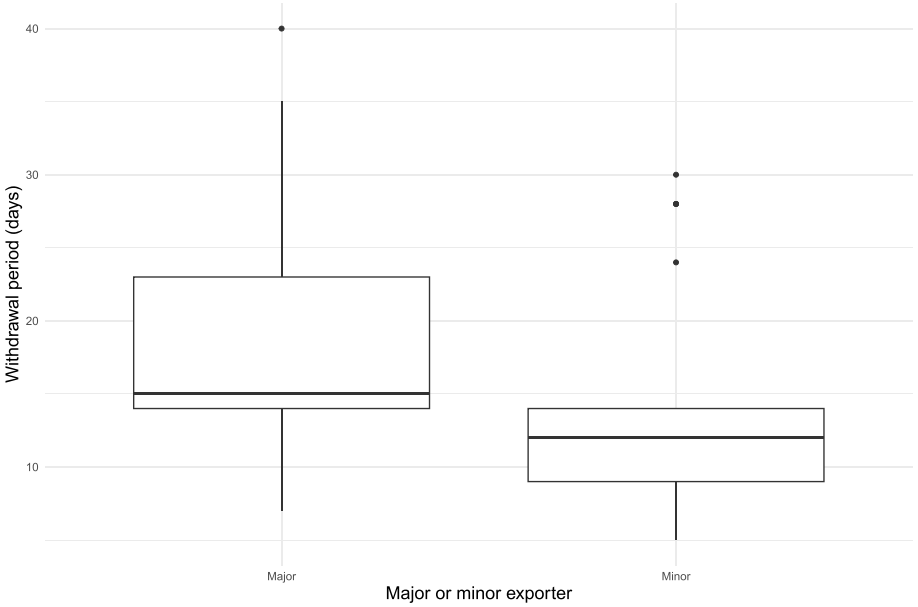

Fig. 2. Boxplot of the withdrawal period related to intramuscular use of 100 mg/ml oxytetracycline in pigs, measured in days, divided into countries defined as either a major (n = 11 and 33 products) or a minor (n = 18 and 35 products) exporter. P = 0.00099 (Wilcox).

comprehensive, and more products may exist within and outside the EU. This is unlikely to affect the results because the inclusion of the 68 products already shows a high degree of variation.

The variations in the withdrawal periods of oxytetracycline 100 mg/ml, ranged from 5 days in Greece to 40 days in Italy. The 35-day difference in withdrawal periods within the EU is perplexing and not justified by the food safety risk. Moreover, the recommended withdrawal period was not identical in all countries for the products marketed under the same brand name. This indicates that the method of establishing withdrawal periods has not been harmonised.

This variation may create a scenario, where the same pig delivered to slaughter after a given number of days after treatment with oxytetracycline could be considered non-compliant in one country and compliant in another, but in fact representing the same consumer risk. To solve this, withdrawal periods should be harmonised. Until this has happened, an exposure assessment as suggested by Alban et al. (2023) should be allowed to estimate the concentration of a VMP at the time of slaughter. This could reduce food waste and improve food security without jeopardising food and consumer safety.

For instance, in Denmark, when withdrawal periods were only determined nationally, a given VMP could only be granted either 6-, 14-, 30- or 60-days withdrawal period, with no possibility in between, which supports the argument for allowing an exposure assessment. Based on this, we hypothesised that the year of the first market authorisation of the product could influence the withdrawal period, but our analysis failed to support this hypothesis. New products registered in the EU

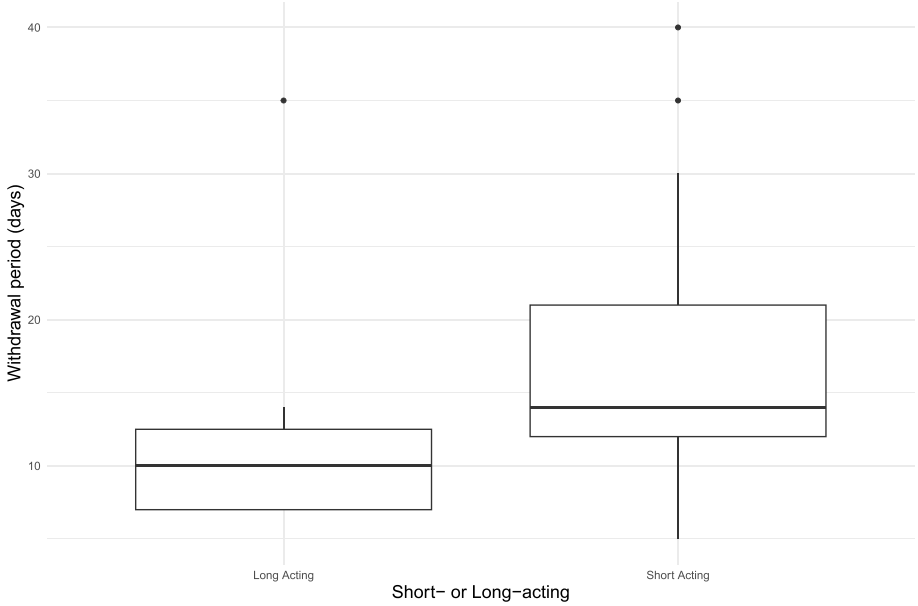

Fig. 3. Boxplot of the withdrawal period related to intramuscular use of 100 mg/ml oxytetracycline in pigs, measured in days, divided into whether the products were long-acting (n = 7) or short-acting (n = 61). P = 0.048 (Wilcox).

today will only have a single withdrawal period for intramuscular use in each species, as the pharmaceutical industry prefers a central authorisation with a specific procedure, thus favouring a harmonisation of withdrawal periods.

Among the investigated factors, two were of significance. The first was the role of export of the country based on the volume of pig meat and the exported proportion. Countries categorised as major exporters of pig meat had significantly longer withdrawal periods than minor exporters. This could be indicative of major exporting countries being more risk averse because they have an export market to protect. Hereby, the abattoirs comply with the legislation of the importing country as well as export audits etc. When exporting products to markets outside of their own region, the exporting countries have an interest in being seen as a reliable source of safe products with a very low acceptance (or zero tolerance) of mistakes such as AM residues exceeding the MRL, to maintain their access to the respective markets. In addition, exporting countries must comply with regulations of the importing country, which can differ, as there is no universal agreement within the area of residues of AM (Léger et al., 2019). An example of this is the MRL for oxytetracycline in pig meat, which is 0.1 mg/kg in the EU, Australia, and New Zealand, and 2 mg/kg in the USA.

The second significant factor investigated was the formulation of the product. Here, it was shown that long-acting products had a shorter withdrawal period than short-acting, which is contra intuitive and confirms that the method of defining a withdrawal period has not been harmonised.

According to the EU legislation, the livestock producer and the abattoir must only market live slaughter animals and products derived from these that have been accompanied by relevant FCI (EU Parliament and Council, 2004 Annex II, Section III). The FCI should include information on the VMP administered to the animals within a relevant period and with a withdrawal period greater than zero. If, based on an evaluation of the received FCI, the Food Business Operator (FBO) concludes that the abattoir has received animals for slaughter, where the withdrawal period has not been observed, the FBO must notify the competent authority (EU Parliament and Council, 2004, Annex II, Section III). A recently conducted RIBMINS survey shows that in many countries, the FCI contains a statement regarding the compliance with the withdrawal period (Li et al., 2023). This is either in combination with reported data on AM use or used alone (Alban et al., 2023).

While the pig producer is responsible for ensuring the accuracy of FCI for a shipment of animals, including compliance with withdrawal periods, it is unrealistic to assume that no mistakes will ever occur. A binary approach to withdrawal periods, compliant or not, simplifies the quality assurance at the FBO level, but does not provide confidence in whether the concentration of residues is, in fact, exceeded. Furthermore, the current approach could, in the worst case, economically discourage pig producers from reporting errors to the FBO, as they can be fined for honesty.

A voluntary test for residues could minimise the consequences of reporting an error, but this practice was abolished within the EU in 2019 (EU Commission, 2019a). This was presumably due to a perceived concern for compliance with the withdrawal periods, i.e., the abattoirs or primary producers putting pressure on the competent authority. Because of this, most EU Members States at the time of reviewing the regulation were in favour of abolishing testing when needed or based on suspicion. However, abolishing the possibility of testing represents a driver for food waste, without any improvement of food safety.

We have focused on intramuscular treatment with oxytetracycline and identified a huge variation in the duration of the withdrawal period. A somewhat similar situation exists for recommended dosages of AMs for oral and parental administration. Here, Postma et al. (2015) identified substantial variations mainly between countries but also some variation within country for the same kind of products. Postma et al. suggested establishment of consensus-defined dosages and provided an example of this for the most used AMs marketed for use in pigs in Belgium, France, Germany and Sweden (Postma et al., 2015). The two main concerns related to dosages of AMs are related to effect of treatment (under-treatment) and development of antimicrobial resistance. In contrast, the variation in withdrawal periods might lead to situations, where meat from a slaughter day is condemned although the MRL would have been complied with.

4.2. Perspectives

While this study focuses on oxytetracycline products with a concentration of 100 mg/ml, a similar variation in withdrawal periods within and between countries may exist for other AMs and VMPs in general. To avoid differences in the pig supply chain, giving priority to a harmonisation process based on the most utilised VMPs is

recommended.

Harmonisation of withdrawal periods for the same kind of product at least across the EU is necessary to ensure consumer safety and to implement sustainability and profitability of animal production. It is unknown whether the inconsistency of the withdrawal periods is random or reflects different levels of risk acceptance. The EU is aware of the issue itself and is striving towards solving it with an increased focus on the harmonisation of human dietary exposure (European Food Safety Authority and European Medicines Agency, 2022). However, the issue of marked differences in the established MRLs between major markets, such as the EU and USA, has not yet been resolved and is not expected to be solved easily as the MRLs diverge between the EU and USA.

Although efforts are being made to harmonise the approval of VMPs and the calculation of human dietary exposure, this will take time. Therefore, an interim solution is also needed because our attention is increasingly shifting towards adhering to the limits imposed by the planet's resources (Steffen et al., 2015). In other words: we need to find ways to carefully consider the risk posed by potential chemical food safety hazards in a systematic, defendable and feasible way and compare it to the risk associated with production of unnecessary wastage of food and animal products. This is a One Health challenge because, on the one hand, countries are wasting food by condemning meat that could be considered safe for consumption e.g., if voluntary testing were allowed and used. This contradicts the European Green Deal's goal of reducing food waste by 50% by 2030 (EU Commission, 2019b). On the other hand, the population should not be exposed to chemical food safety hazards, which could undermine the credibility of the pig industry.

Consequently, this paper supports a risk-based strategy in meat inspection, with the possibility to determine whether the ADI is exceeded. Instead of following a linear progression from ADI to MRL to withdrawal period, incorporating safety margins at each stage, in critical situations, such as when a pig producer contacts the abattoir about early delivery of pigs, we propose utilising the approach suggested by Alban et al. (2023). This approach considers the half-life of the substance, the duration between the animal was treated and slaughtered, as well as the daily serving size likely to be consumed. Because this approach approximates real-life scenarios, it remains applicable to most of the situations in which voluntary testing could have been applied. The approach requires that the FBO and local competent authority are trained to perform the calculations and able to draw a conclusion from the results. As an aid for this, an interactive exposure risk model has been developed. It can be found on: https://ribmins.com/survey-on-residues-of-antimicrobials-in-pigs/. The resulting process may be considered a time-consuming but worthwhile investment considering the benefits of more primary producers admitting their mistakes, reduced food waste, and equal treatment of pig producers in the EU. This would also be in line with systems thinking approach, favouring positive feedback systems, to push players in the system to do what is best for the whole system (Anderson & Johnson, 1997). In fact, this is a behaviour that we want to reinforce to create self-learning meat value chains.

5. Conclusion

Our survey identified that a minimum, median, and maximum withdrawal period of 5, 14 and 40 days, respectively, are in force for oxytetracycline 100 mg/ml for intramuscular use in pigs in 29 countries in- and outside the EU. This indicates that the withdrawal periods of this kind of product vary more than scientifically justified. The first significant contributing factor for explaining this variation was whether the country was a major or minor pig meat exporter. Neither the regional location within Europe, nor the year of the product authorisation were found to have a significant effect on the duration of the withdrawal period. The other significant contributing factor was whether the product was long- or short-acting. The finding that long-acting products were associated with a shorter withdrawal period than short-acting products further points to the need for updated and harmonised withdrawal periods.

The reason for the observed variation is the prior lack of a harmonised approach to determine the withdrawal periods. Until the withdrawal periods are harmonised, we suggest using a risk-based approach to calculate the actual concentration of a given VMP at the time of slaughter when an animal is accidently delivered prematurely. In this way, the concentration can be compared with the MRL. If it is higher than MRL, safe ways of handling can be identified through intended use compared to the ADI.

CRediT authorship contribution statement

Daniel Hjorth Lund: Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Investigation, Visualization. **Jesper Valentin Petersen:** Writing – review & editing. **Boris Antunovic:** Writing – review & editing. **Madalina Belous:** Writing – review & editing. **Silvia Bonardi:** Writing – review & editing. **Rosa Maria García-Gimeno:** Writing – review & editing. **Ian Jenson:** Writing – original draft, Writing – review & editing. **Arja H. Kautto:** Writing – review & editing. **Michał Majewski:** Writing – review & editing. **Derk Oorburg:** Writing – review & editing. **Ioannis Sakaridis:** Writing – review & editing. **Alexandrina Sirbu:** Writing – review & editing. **Madalena Vieira-Pinto:** Writing – review & editing. **Ivar Vågsholm:** Writing – review & editing. **Lis Alban:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Jesper Valentin Petersen and Lis Alban work for an organisation which advises farmers and meat-producing companies.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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