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Prioritizing veterinary drug residues in animal products for risk-based monitoring

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ABSTRACT

The EU Official Controls Regulation (EU) 2017/625 (OCR) requires a risk-based monitoring program for veterinary drug residues in animal products. The aim of this research was to rank various substances in animal products as input for such a Multi-Annual National Control Plan (MANCP). Previously derived decision trees were used to prioritize a total of 438 substances and 5228 substance-product combinations. The prioritization incorporated information on non-compliances, use of veterinary drugs and potential human health effects. Overall, the majority of the unauthorised substances (63%) were classified as high priority, although there are distinct differences between substance groups. For the authorised substances, around 27% were classified as low priority, 17% as medium priority and 12% as high priority. For the remaining substances, there was a lack of data resulting in the recommendation to start a survey. The evaluation revealed that not all relevant substance-product combinations are currently included in the MANCP and data or information on (potential) use is often difficult to retrieve. Overall, the decision trees provided a successful tool to classify substances in low, medium and high priority to include in the MANCP and the approach could be applied by other EU MS as input to their risk-based monitoring programs.

1. Introduction

Animals kept for livestock production may become ill and require treatment with veterinary drugs. These veterinary medicines cover a wide range of antibiotics, antiparasitic and antifungal drugs, hormones and anti-inflammatory drugs. Since their introduction in the 1930s, antimicrobial substances have frequently been used in animal production, not only for health reasons but also to increase productivity (Kirchhelle, 2018). Increasing concerns regarding antibiotic resistance development led to a phasing-out and an ultimate ban on their use for growth-promoting reasons (Regulation (EC) 1831/2003). As of 28 January 2022, rules on therapeutic use were tightened, limiting possibilities for prophylactic and group treatments (Regulation EU) 2019/6). Although veterinary antibiotic use between 2011 and 2020 declined by 43% in the EU (Nuna, 2022), global antibiotics use in animals is projected to increase (Patel et al., 2020). Global antimicrobial use was estimated to be around 100,000 tonnes in 2020 and expected to increase by 8% in 2030 (Mulchandani et al., 2023). Besides antibiotics, other veterinary drugs like antiparasitics, coccidiostats and nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used in livestock production (Rana et al., 2019). A major application of antiparasitics concerns the management and treatment of infections with gastro-intestinal worms, or helminths, which is primarily relying on benzimidazoles and avermectins. Treatment of ectoparasites is often based on substances also referred to as insecticides, e.g. pyrethroids, which are (chemically and regulatorily) at the interface with the pesticides domain. Coccidiostats can also be considered antiparasitics, since they target protozoan parasites, but they are often distinguished because of their regulatory classification as feed additives (Regulation (EC) No 1831/2003). NSAIDs are the primary class of drug for reducing inflammation and pain relief in animals. Additionally, unauthorised substances, such as hormones and beta-agonists, can be used to promote growth or feed conversion rate. In the EU, their use has been banned since 1988 (Directive 88/146/EEC) but other countries such as the US and Australia allow a restricted use (Stephany, 2010). The use of both authorised and prohibited veterinary drugs may lead to the presence of residues in animal products such as meat, milk and eggs. Since these residues may impact human health, the EU evolved an elaborate

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framework of food monitoring and surveillance.

Until 2022, Directive 96/23/EC described the monitoring of veterinary drug residues in animal products. As of 2022, this was repealed by Regulation (EU) 2017/625, which is a more comprehensive dictate essentially dealing with official controls in all areas of food production. Article 9 of this regulation states that official controls should be performed on a risk basis with appropriate frequency. However, the regulation does not provide guidance on how to derive such risk-based control programs. Therefore, methods are needed to prioritize veterinary drugs so that decisions regarding substances to be included in a risk-based Multi-Annual National Control Plan (MANCP) can be substantiated. Regulation (EU) 2017/625 defines risk as "a function of the probability of an adverse effect on human, animal or plant health, animal welfare or the environment and of the severity of that effect, consequential to a hazard". Since we anticipated that the evaluation of all these elements into one prioritization method would be overly complex, we decided to focus our study on the risks related to human health only.

Various methods are available to prioritize risks. These can be either qualitative, semi-quantitative or quantitative. Qualitative methods are methods that do not require calculations. They are easy to apply and require limited time and budget. Examples are the use of expert judgement or decision trees. In quantitative methods, the risks for human health are calculated using estimations for exposure to the hazard and severity of the hazard. Examples are full risk assessments or risk ratio methods based on calculating a hazard quotient. The advantage of such quantitative methods are that they are objective and transparent. However, they require a large amount of data and are time consuming. Semi-quantitative methods are methods in-between qualitative and quantitative methods and are usually based on scores for probability and severity of the hazards. An example is the risk matrix method. Depending on the required output, time and budget available, one of these approaches can be selected for risk ranking (Van der Fels-Klerx et al., 2018). Since the number of substance-product combinations to be evaluated in the context of a MANCP is very large and available data is limited, previously a qualitative method for prioritization was developed (van Asselt et al., 2018). This method consists of decision trees for authorised and prohibited substances and includes questions related to non-compliances of the substances in animal products, their use in livestock production and their potential human health effects. The decision trees yield a prioritization of substances into low, medium and high priority to include in the MANCP (van Asselt et al., 2018).

The new Control Regulation ((EU) 2017/625) requires a risk-based MANCP. However, currently, there is no guidance on how to establish such a risk-based monitoring program. Therefore, the aim of the current study was to evaluate and rank veterinary drug residues in animal products using the predefined decision trees. The outcome provides valuable input for the realization of a risk-based monitoring program and can be used by other EU MS to establish their MANCP according to the new Control Regulation as well.

2. Materials and methods

In the period 2018–2021, all substance groups mentioned in the latest draft Implementing Regulation (i.e. SANTE 11987-2017 Rev 9) were evaluated for all animal species and products as indicated in the former Directive 96/23/EC, i.e. bovine, porcine, poultry, horse, goat, sheep, milk, eggs, aquaculture (fish and shellfish), farmed game (mammals and poultry), rabbits and honey. This evaluation was performed within various research projects commissioned by the Netherlands Food and Consumer Product Safety Authority (NVWA) and funded by the Dutch Ministry of Agriculture, Nature and Food Quality (LNV). For detailed information on the approach followed, we refer to the reports published for each of these projects (Pikkemaat et al., 2022, p. 162; van Asselt et al., 2019, 2020, 2021, p. 275). The prioritization was performed for the Netherlands with data used from other EU MS as well. This paper summarises the results obtained and the lessons learned.

2.1. Substances included in the prioritization

At the time of the study, the latest draft Implementing Regulation (i.e. SANTE 11987-2017 Rev 9) was used to determine which substance groups for each animal species or product is to be included in the MANCP. Table 1 represents the substance groups included in this study. The Implementing Regulation became into force on 7 July 2022 as Commission Delegated Regulation (EU) 2022/1644. The most notable difference with the draft Implementing Regulation used in our study is the addition of antiviral substances as substance group. As this information was not available at the time of our study, these substances were not evaluated in our research. Substance groups in Regulation (EU) 2022/1644 are classified as either prohibited/unauthorised (group A substances) or authorised substances (group B substances). For the authorised B category, the substances to be included within a substance group were based on Regulation (EU) 37/2010 Table 1. Table 2 of this regulation was used for the substances defined as group A2 of the Implementing Regulation. For the other unauthorised substance groups, substances currently monitored in the MANCP were included, complemented with substances included in the EURL guidance document on prohibited or unauthorised pharmacologically active substances (EURL, 2020, p. 9). In case non-compliances were reported in EFSA reports or the Rapid Alert System for Food and Feed (RASFF) on specific substances not yet included, these were added as well. Additionally, substances available for treatment of non-food producing animals (https://www.diergeneesmiddeleninformatiebank.nl/) were added. More substances were retrieved from information on US, Australian and Chinese maximum residue limits and approved feed additives. Specifically for

Table 1
Substance groups included in the prioritization.

Group	Definition
GROUP A – Prohibited or unauthorised pharmacologically active substances, used on food producing animals	
A1a	Stilbenes
A1b	Antithyroid agents
A1v	Steroids
A1d	Resorcylic acid lactones, including zeranol
A1e	Beta-agonists
A2	Prohibited substances, listed in of the Annex to Regulation (EU) No 37/2010
A3a	Dyes
A3b	Pesticides and biocides as defined in Reg. (EU) No 1107/2009[a] and biocides as defined in Reg. (EU) No 528/2012[b], which may be used in animal husbandry of food-producing animals
A3c	Antimicrobial substances
A3d	Coccidiostats and histomonostats
A3e	Protein and peptide hormones
A3f	Any other pharmacologically active substance not listed in Table 1 of the Annex to Regulation (EU) No 37/2010 or not authorised according to Regulation (EU) No 1831/2003 and which may be misused on food producing animals. In this study, we included unauthorised sedatives and NSAIDs in this group
GROUP B – Pharmacologically active substances authorised for the use in food producing animals according to Union legislation	
B1a	Antimicrobial substances
B1b	Insecticides, fungicides, anthelmintics and anti-parasite agents
B1c	Sedatives
B1d	Non-steroidal anti-inflammatory drugs (NSAIDs)
B1e	Other pharmacologically active substances listed in Table 1 of the Annex to Regulation (EU) No 37/2010. In this study, we included authorised steroids and beta-agonists in this group
B2	Coccidiostats and histomonostats authorised according to Regulation (EU) No 1831/2003, for which MRLs are set under Union legislation and for which maximum levels are set under Regulation (EC) No 124/2009

[a] OJ L 309, 24.11.2009, p. 1.
[b] OJ L 250, 15.9.2012, p. 17.

horse, the list of substances essential for treating horses as indicated in Regulation (EU) 122/2013 was used to complete the list of substances. Some of the substances may have an activity spectrum surpassing a single pharmaceutical class, which makes their classification into a certain group sometimes somewhat arbitrary. The substances we included in each substance group for the prioritization are indicated in the supplemental material (Annex 2).

2.2. Decision tree I - group A substances (prohibited or unauthorised substances)

The established list of prohibited or unauthorised substances was evaluated using the previously derived decision tree for prohibited/unauthorised substances (*van Asselt* et al., *2018*). The decision tree was adapted slightly to also allow for unknown answers in case of limited data/information (Fig. 1). Each question was answered using the information below. All possible answers and the subsequent conclusions are depicted in Annex 1 of the supplemental material.

1. Were any non-compliant residue data of the substance found in the last five years?
   Monitoring data on residues of the substances were used to answer this question. EFSA reports were used to identify non-compliances in EU MS (EFSA, 2014, 2015, 2016, 2017, 2018, 2019, 2020) as well as RASFF notifications (2012–2020, https://webgate.ec.europa.eu/rasff-window/portal). Furthermore, national monitoring data were extracted from the Dutch Quality Program for Agricultural Products (ChemKAP; https://www.rivm.nl/en/chemkap). Data originated from Wageningen Food Safety Research (WFSR) and was available for the years 2012–2019.
2. Is a human health risk due to residues of the substance scientifically proven to be absent or negligible?
   Available information from authorities in Europe or the US (i.e. EFSA, JECFA or EMA reports) as well as scientific papers were used to determine the effect of the substance on human health. In case no severe and/or irreversible adverse effects were reported, this question was answered positively. When conclusions were conflicting, EU Opinions were leading to reach a final conclusion.

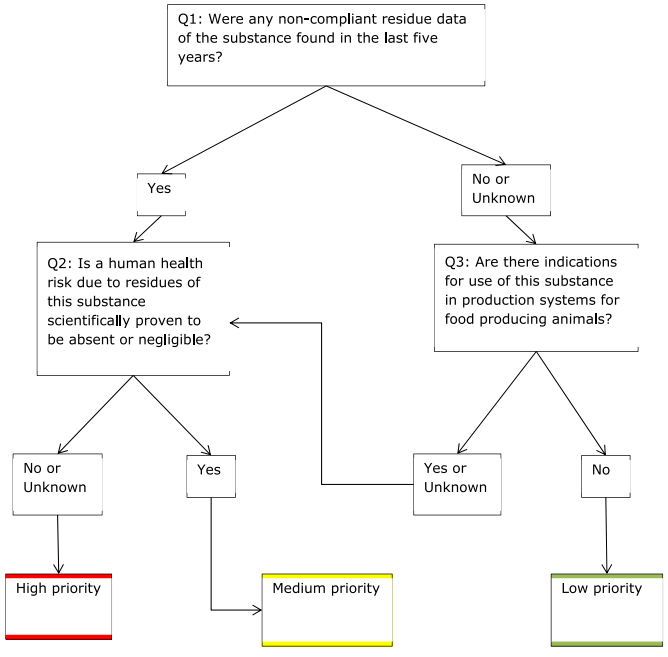

Fig. 1. Decision tree I for unauthorised substances (updated from van Asselt et al. (2018)).

3. Are there indications for use of this substance in production systems for food producing animals?
   Several sources of information were used to answer this question:
   - Non-compliances in other animals were checked using the following approach:
     - o non-compliances in other mammals except horse were seen as indication of use for bovine, porcine, goat and sheep;
     - o non-compliances in all other mammals was seen as indication for use in horse;
     - o non-compliances in other milk-producing animals (goat, sheep) and non-compliances in bovine were seen as indication for use in dairy cows (milk)
     - o non-compliances in poultry was seen as indication for use in laying hens (eggs) and vice versa;
     - o non-compliances in poultry was seen as indication for use in game-poultry.
   - Registrations in the US were evaluated using the FDA database (www.animaldrugsatfda.fda.gov) and the Code of Federal Regulations (CFR) Title 21 part 556 and 558 (https://www.accessdata.fda.gov/). If products are registered in the US, the substance was assumed to be available on the market. For unauthorised pesticides (A3b), antimicrobials (A3c) and coccidiostats (A3d), additionally the Chinese national food safety standard (Ministry of Agriculture and Rural Affairs of China et al., 2019) was checked as well as additional sources for approvals outside the EU.
   - Registrations in the EU for companion animals were evaluated using the Dutch database of the Medicines Evaluation Board of the College ter Beoordeling van Geneesmiddelen (CBG-MEB), https://www.diergeneesmiddeleninformatiebank.nl/) as well as available databases from other EU countries (www.vetcompendium.be, www.vetidata.de, www.vmd.defra.gov.uk, www.ircp.anmv.anses.fr) and the EU Veterinary Medicines Information Website (https://medicines.health.europa.eu/), of which at the moment of access the content was limited to registrations authorised by the EC, and the Competent Authorities of Ireland and Denmark. In case registrations for horse were found, Q3 was answered positively for horse irrespective of whether the product is allowed for horses not intended for human consumption.
   - Online availability was checked on online marketplaces such as alibaba.com and ebay.com. For the steroids, websites for anabolic steroids were screened such as anabolenpowers.com, steroiden.com and anabolenkopen24.nl. In case products were available that can be used as such in animals (e.g. injections), the availability was answered as "Y". However, in case, a potential use was unlikely (e.g. only available as injectables resulting in unlikely use in poultry), the availability was answered as "Unl.".

2.3. Decision tree II – group B substances (authorised substances)

The established list of authorised substances was evaluated using the decision tree for authorised substances based on (van Asselt et al., 2018) (Fig. 2). Each question was answered using the information below. All possible answers and the subsequent conclusions are depicted in Annex 1 of the supplemental material.

1. Is this an essential antimicrobial for humans?
   This question was only relevant for group B1b (authorised antibiotics). For this question, the 2017 WHO report was used to identify the highest priority critically important (HPCI) antimicrobials for human medicine. These antimicrobials included quinolones, 3rd and higher generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins (WHO, 2017, p. 48).
2. Have MRLs been set for this substance in this animal species or for this animal product?
   This question was answered using Table 1 in the Annex of Regulation (EU) 37/2010. The extrapolation of MRLs in species with MRLs to

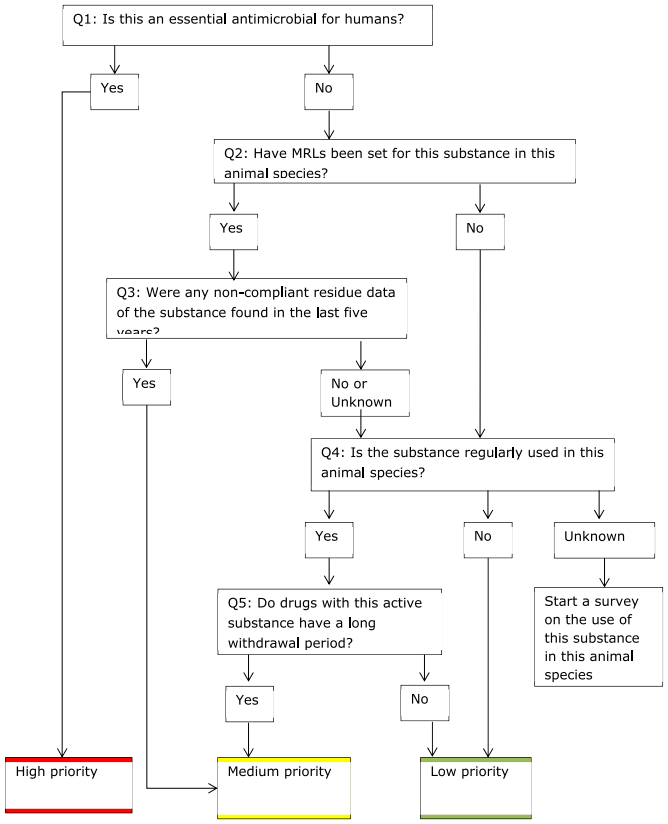

Fig. 2. Decision tree II for authorised substances (updated from van Asselt et al. (2018)).

species without MRLs as outlined in Regulation (EU) 2017/880 was not taken into account. Therefore, if no MRL was indicated for the animal product in Regulation (EU) 37/2010, the question was answered negatively.

3. Were any non-compliant residue data of the substance found in the last five years?
   In order to answer this question, the same data sources were used as indicated under question 1 for the decision tree on prohibited/unauthorised substances.
4. Is the substance regularly used in this animal species?
   Several information sources were used to answer this question:
   - Non-compliance data for the specified animal species or related species (as indicated under Q3 of decision tree I).
   - Reports on detection results of the active substance at levels below the MRL for the specified animal species.
   - Veterinary drug registrations for the specified animal species were queried from the same databases as indicated above for companion animals, i.e. the Dutch CBG-MEB (https://www.diergeneesmiddeleninformatiebank.nl/) as well as available databases from other EU countries (www.vetcompendium.be, www.vetidata.de, www.vmd.defra.gov.uk, www.ircp.anmv.anses.fr) and the EU Veterinary Medicines Information Website (https://medicines.health.europa.eu/), of which at the moment of access the content was limited to registrations authorised by the EC, and the Competent Authorities of Ireland and Denmark. In case registrations for horse were found, Q3 was answered positively for horse irrespective of whether the product is allowed for horses not intended for human consumption.
   - Registered antibiotics use by the Netherlands Veterinary Medicines Institute (SDa, https://www.autoriteitdiergeneesmiddelen.nl) for 2017. As a cut-off value, a DDDA ("Defined Daily Dose Animal", the defined average dose of a specified medicine per kg of a specified animal per day (EMA, 2015; Postma et al., 2014)) of 50,000 was set. This threshold was set such that at least 95% of the total antibiotics use in each of the animal species would be included in the analyses. Since the SDa data only indicated antibiotics use in poultry, no distinction could be made between use for broilers and use for laying hens. As a result, it was assumed that antibiotics use for poultry meat and eggs was the same (worst case assumption).
   - Sales data from the Dutch Association of Manufacturers and Importers of Veterinary Medicinal Products (FIDIN) for 2019 were consulted. FIDIN data were available for most food producing species except for aquaculture, farmed game, rabbits and bees. However, since registrations for goat and sheep are usually also registered for cows, a distinction in sales data specific for these animal species was not possible. Furthermore, sales data for cows include both beef cattle and dairy cows and sales data for poultry include both broilers and laying hens. In case a distinction for a specific animal species was not possible, a worst-case approach was used meaning that sales data were attributed to all species indicated. For example, in case 100 kg of substance A was sold in 2019 with a registration for poultry, this number was used as input both for broilers and for laying hens. The following thresholds were used (based on median values):
     - o antibiotics, antiparasitics, NSAIDs and coccidiostats: 150 kg for bovine, porcine and poultry;
     - o antibiotics, antiparasitics, NSAIDs and coccidiostats: 65 kg for horse, goat and sheep;
     - o beta-agonists, sedatives and steroids: 10 kg for all food producing species.

For aquaculture, farmed game, rabbits and honey, limited information was available. To circumvent this, authorised substances for relevant countries and likely use of the substance based on internet search. Google searches were performed to find indications of use focusing on the time period 2011–2021. As search terms the name of the substance was included as well as the animal species. For aquaculture for some substance groups or individual substances additional search terms like parasite, sea lice or infection treatments were included, as the primary search yield mainly ecotoxicology studies. Pharmacokinetic studies were not considered as indication of use if no additional supporting evidence (e.g. marketable products) was found. Besides scientific literature, internet fora were consulted and products mentioned on veterinary websites. Specific attention was also given to veterinary websites which included recommended veterinary products and dosages for animal species.

5. Do drugs with this active substance have a long withdrawal period?

Withdrawal periods were obtained from the product specifications retrieved from the Veterinary Medicinal Products (VMP) database of the Medicines Evaluation Board of the *College ter Beoordeling van Geneesmiddelen* (CBG-MEB) database. In case the longest withdrawal time was longer than 10 days for beef, pork, rabbit and poultry meat and longer than 5 days for milk and eggs (Danaher et al., 2016), this question was answered with a 'yes'.

3. Results

For the main livestock production species, i.e. bovine (meat and milk), porcine, poultry (meat and eggs), horse, goat and sheep, all substance groups were evaluated. For aquaculture, farmed game, rabbits and honey, only those substance groups that were indicated to be included for these animal species in the latest draft Implementing Regulation (i.e. SANTE 11987-2017 Rev 9) were evaluated.

3.1. Prohibited or unauthorised substances (group A substances)

Based on the available information, the questions in decision tree I were answered in order to prioritize the Group A substances. In total, 273 substances were evaluated, i.e. 4 stilbenes (group A1a), 8 antithyroid agents (group A1b), 36 steroids (group A1c), 6 resorcyclic acid lactones (RALs, group A1d), 38 beta-agonists (group A1e), 13 prohibited substances (group A2), 5 dyes (group A3a), 28 unauthorised pesticides and biocides (group A3b), 36 unauthorised antimicrobial substances (group A3c), 30 unauthorised coccidiostats and histomonostats (group A3d), 14 protein and peptide hormones (group A3e), 37 unauthorised sedatives (group A3f) and 18 unauthorised NSAIDS (group A3f). All substances were classified as low, medium or high priority to include in the MANCP based on the outcome of the decision tree. In some cases, there was a lack of monitoring data hampering a final conclusion. Questions 1 and 3 in the decision tree were then answered with 'unknown' resulting in a medium or high priority based on the human health effects evaluated in Q2 of the decision tree. A proviso (#) was added to differentiate these outcomes from substances that were classified as medium or high based on available data. This resulted in around 39% of all substances with a proviso. Game mammals in this respect had the highest number of uncertainties in the evaluation. The final outcome per substance group for the group A substances is depicted in Figs. 3–5. The evaluation per individual substance can be found in the supplemental material (Annex 2). The figures show that, overall, the majority of the prohibited or unauthorised substances (63%) were classified as high priority (with or without provisos) although there are distinct differences between substance groups. Almost 93% of the group A2 substances were classified as high priority although half of these were the result from a lack of data. On the other hand, almost half of the group A1 substances obtained a low priority since no non-compliances were found or use of the substance in the animal species was unlikely. This was primarily the case for the beta-agonists. The only medium priority results were obtained for the group A3 substances. For most substances, a human health effect could not be excluded resulting in a high priority. For some antiparasitics, antimicrobials and NSAIDs, evidence was found that human health effects due to residues of the substance were negligible resulting in a medium priority.

3.2. Authorised substances (group B)

For the Group B substances, the questions in decision tree II were answered based on all available information. In total, 169 authorised substances were classified: 74 antibiotics (group B1a), 43 insecticides (group B1b), 14 sedatives (group B1c), 13 NSAIDs (group B1d), 10 other substances (group B1e) and 15 coccidiostats (group B2). Only antibiotics that were classified by the WHO as highest priority critically important (WHO, 2017, p. 48) were evaluated as high priority. In case of limited monitoring data or information on potential use, the recommendation is

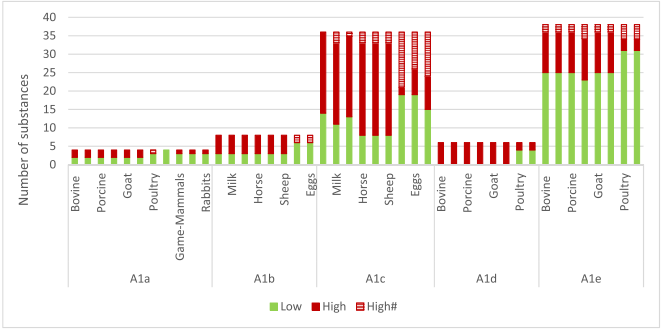

Fig. 3. Overview of prioritization of stilbenes (A1a), Antithyroid agents (A1b), Steroids (A1c), RAL (A1d) and beta-agonists (A1e); High# indicates the substance was classified as high priority due to a lack of data.

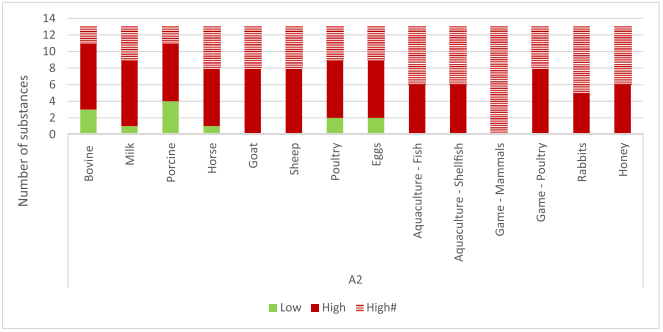

Fig. 4. Overview of prioritization of substances in group A2 (prohibited substances included in Table 2 of the annex of Regulation (EU) 37/2010); high# indicates the substance was classified as high priority due to a lack of data.

to start a survey. Substances for which indications of use were found were marked with an asterisk. It is recommended to include these substances in a survey to obtain (potential) prevalence data. The results for each substance group are depicted in Fig. 6. Overall, 27% of the authorised substances were classified as low priority, 17% as medium priority and 12% as high priority. For 44% of the substances, it was recommended to start a survey because of a lack of data. The percentage of substances for which it was recommended to start a survey differed per animal species: around 25% of the substances for the main livestock species were classified as 'start survey' (with or without asterisk), whereas the majority of substances for aquaculture, farmed game and rabbits (around 75%) were classified as 'start survey'. The prioritization at substance level is provided in the supplemental material (Annex 2).

4. Discussion

The results in this study showed the decision trees to be a successful tool for prioritization of substances into low, medium and high priority to include in the MANCP. However, the proposed procedure did have some limitations. Not all substances evaluated are currently included in the Dutch or other EU MS monitoring programs; subsequently, for these substances, monitoring data are lacking by definition. The consequence of the approach that was followed in our study is that many substances had to be classified as 'medium/high#' for the prohibited substances and as 'start survey' for the authorised substances in case of data gaps. This was especially the case for aquaculture, farmed game, rabbits and honey. A more accurate prioritization of substances is possible when the advice to "start survey" is effectuated and when medium/high# substances are included in the monitoring as this will result in additional prevalence data.

Furthermore, in future monitoring approaches it would be beneficial to replace the current analytical methods using a targeted approach (LC-MS) with broad screening methods (LC-HRMS). Its potential has already been demonstrated in multiple applications (Desmarchelier et al., 2022; Jansen et al., 2022; Kaufmann et al., 2023). Using untargeted methods will open the possibility to retrospectively search data for compounds on which currently information is lacking (Turnipseed et al., 2019). This data could then directly feed the updated prioritization (the current data gaps) and aid in risk based monitoring (Jongedijk et al., 2023).

Besides the potential of broad screening and retrospective analysis, in some cases, it was also difficult to determine whether the absence of non-compliances means that a substance is not found in the monitoring programs or that it is not included in the scope of the analytical methods. The outcome of the prioritization would further gain accuracy if knowledge on the monitoring scope would become accessible, including all substances analysed and not only non-compliant results. In our analysis, we were able to use information on levels of authorised substances found below the MRLs as input to the question related to potential use (Q4 in Fig. 2). However, this information was only available

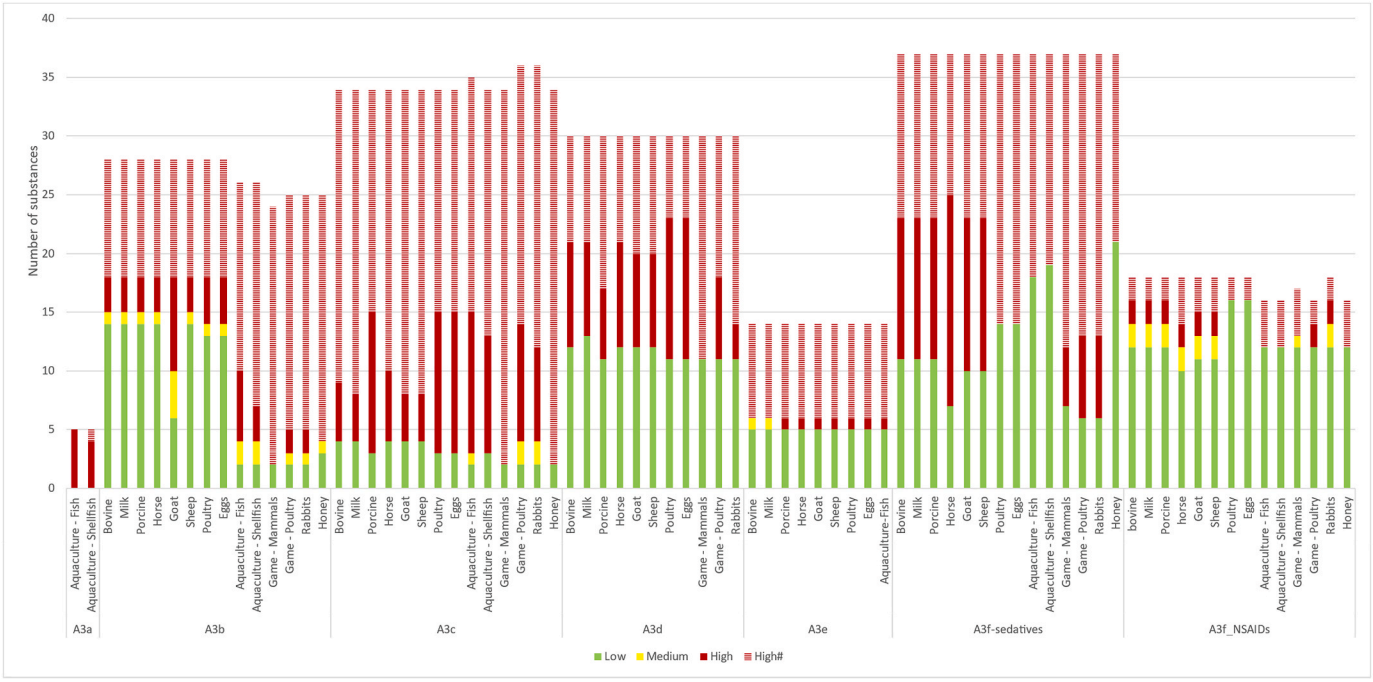

Fig. 5. Overview of prioritization of unauthorised dyes (group A3a), antiparasitics (group A3b), antimicrobials (A3c), coccidiostats (group A3d) protein and peptide hormones (group A3e), sedatives (group A3f) and NSAIDs (group A3f); high# indicates the substance was classified as high priority due to a lack of data.

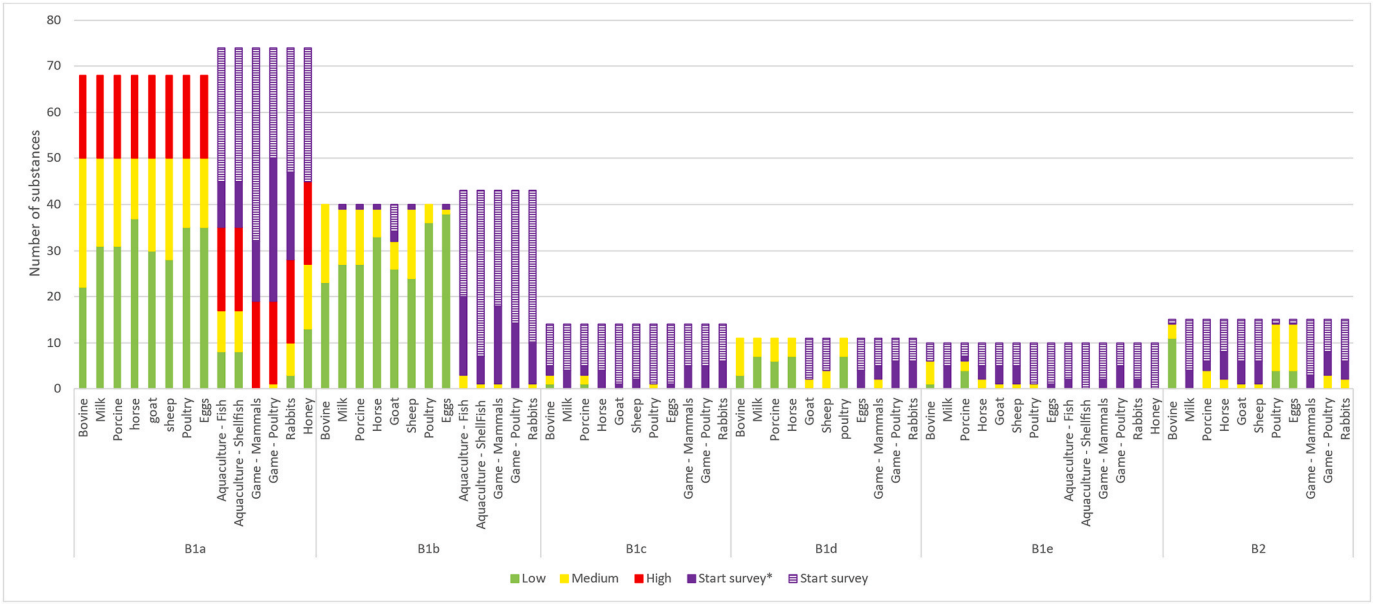

Fig. 6. Overview of prioritization of authorised antibiotics (group B1a), antiparasitics (group B1b), sedatives (group B1c), NSAIDs (group B1d), other authorised substances (group B1e) and coccidiostats (group B2); Start survey indicates that substances are currently not included in the MANCP and therefore there is a lack of data. Start survey* indicates that there are indications that residues may be found due to potential use or non-compliances found in related species.

for the Netherlands. The annual EFSA reports on monitoring currently only comprise non-compliances. Prevalence data of all residues detected (so above the reporting limits) would much improve accuracy of the prioritization. This could be achieved if all countries could provide monitoring information below MRL (e.g. at 1/10 MRL). Another complication when evaluating monitoring data is that some of the antiparasitics are also applied as pesticides. From a residue monitoring perspective, it is impossible to determine whether residues originate from (illegal) use as a veterinary medicinal product, or occasional environmental exposure, either through treatment of e.g. housing, or transfer from feed through use as plant protection.

If a substance was presumed not to be included in the scope of the monitoring, potential use in the animal species was evaluated according to Q3 and Q4 for prohibited and authorised substances, respectively. These questions included, but were not limited to, assessments of registered veterinary drugs (in EU countries) and online availability worldwide since the easy accessibility of regulated or prohibited substances may contribute to an increased potential use. The information obtained in this evaluation is, however, prone to under- or over-estimations. Underestimations could be introduced based on the type of

information sources and the language used as the information sources for registered veterinary drugs were limited to available databases of the western EU member states, and online searches were in most cases solely performed in English. Both could result in missing potentially valuable data that could indicate the ease of purchase of regulated or prohibited substances. On the other hand, overestimations could be introduced by the same questions, since the ease of purchase does not in all cases imply actual use. Furthermore, this type of data gathering could potentially be affected by biases especially when information quality could not be verified (e.g. information obtained from internet fora). Additionally, non-compliances in a certain animal species were used as potential VMP use in other animal species. For example, non-compliances in poultry were considered as potential use in laying hens. These assumptions may also have led to overestimations. Reducing these possible under- or overestimations for the potential use is challenging, but minimization was attempted by including multiple sub-questions for assessing the potential use. The final evaluation of these sub-questions was obtained based on multiple expert discussions. For the authorised substances, the evaluation of VMP use will become easier in the future as data on the use of authorised substances are likely to become available due to the implementation of the new Regulation (EU) 2021/578, which prescribes the requirements for registering VMP sales and use.

Despite the limitations and potential improvements indicated above, the evaluation performed in this study did reveal that a prioritization of a wide range of veterinary drugs in various animal products is possible. The methodology followed was structured and transparent which allows to follow the decisions made during the procedure. It also enabled to pinpoint to data gaps that may be filled by performing surveys. Finally, although the method was applied for the Netherlands, the methodology followed may also be useful for other EU MS. The methodology followed was based on decision trees to prioritize substances in the various animal species. Other methods are also available for prioritization, such as scoring methods, risk matrices or multi-criteria decision analysis (Van der Fels-Klerx et al., 2018). These methods, however, require quantitative data as well as thresholds to establish scores for the prioritization. The complexity of the current evaluation, in which a large number of substances and animal species were evaluated, did not allow the use of these methods for risk ranking. Alternatively, expert elicitation can be used for risk ranking as an example of a qualitative risk ranking method. The downside of that method, however, is that biases may be introduced due to inappropriate selection of the experts, the explanation of the assignment to be completed and the process to combine the obtained range of opinions (Van der Fels-Klerx et al., 2018). The decision trees used in this study are in essence easy to apply although the inclusion of sub-questions and the evaluation of the various information sources in this research showed that the prioritization process was laborious. In the future, machine learning techniques may help to evaluate the questions in the decision trees. These techniques may be applied for the questions related to non-compliances and VMP sales data although a manual evaluation will remain necessary for interpretation purposes. The advantage of the decision trees is that the output can be easily communicated to food safety authorities responsible for designing monitoring plans. As such, the use of decision trees allows for a structured and transparent approach, especially when all underlying decisions are recorded, and can be used as input to a risk-based MANCP. Nevertheless, part of the MANCP should be random in order to obtain representative data as is also indicated in Regulation (EU) 2022/1644. Which substances are finally taken up in the MANCP not only depends on the risk prioritization but also on the feasibility of including high priority substances and on other elements such as cost estimates or political reasons. The risk manager is responsible for weighing the several factors and finalising the MANCP (Aven, 2016). The evaluation performed in this research provides the scientific background that can be used as one of the inputs for drafting the MANCP.

5. Conclusions and recommendations

The decision trees applied in this research allowed for the prioritization of substances into low, medium and high priority to include in the MANCP. Although the use of the decision trees was primarily based on national monitoring data, the inclusion of EFSA data and RASFF notifications combined with the wide approach applied to answer the other questions, make the outcome valuable for other EU MS as well. And even though the current prioritization was obviously 'EU-centric', we think the methodology can be applied outside Europe as well when using locally available data. In our study, we did our best to include, from a global perspective, as many veterinary relevant substances as possible and the question on "indications of use" was answered from a global perspective as well. For our evaluation, it is recommended to at least include the high priority substances in a risk based MANCP. In many cases, multi-residue analyses methods form the core of monitoring. Inevitably, also low and medium priority substances will be in the scope of the applied methods. Obviously, these should not be removed from the analysis. Existing data gaps should be addressed by starting surveys for group B substances and including substances that obtained provisos for group A into the monitoring program. This could be simplified when future monitoring methods start applying untargeted screening, as then previously derived data could be surveyed retrospectively. Furthermore, providing data below MRL would also help filling part of the data gaps. Broader availability of consumption data on authorised veterinary drugs will also improve the accuracy of the answers to the questions in the decision trees. Once more data become available, e.g. when substances currently not included in the monitoring program are monitored and when data on veterinary drug use becomes available, a more accurate prioritization of the substances is possible. It is, therefore, recommended to regularly update, for example, every 5 years, the prioritization in order to include the latest information available.

CRediT authorship contribution statement

E.D. van Asselt: Conceptualization, Methodology, Validation, Investigation, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition. **J. Jager:** Conceptualization, Methodology, Investigation, Writing – original draft. **L.J.M. Jansen:** Conceptualization, Methodology, Investigation, Writing – original draft. **E.F. Hoek-van den Hil:** Conceptualization, Methodology, Investigation, Writing – review & editing. **I. Barbu:** Investigation, Writing – review & editing. **P. Rutgers:** Investigation, Writing – review & editing. **M.G. Pikkemaat:** Conceptualization, Methodology, Validation, Investigation, Writing – original draft, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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