17 February 2021
EMA/CVMP/ERA/268948/2020
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on the "Reflection paper on antimicrobials in the environment: considerations for current and future risk assessment of veterinary medicinal products" (EMA/CVMP/ERA/632109/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Andreu Rico (IMDEA Water)
2	Health Care Without Harm Europe (HCWH)
3	Federation of Veterinarians of Europe (FVE)
4	Prof Dr Marc Heyndrickx, Flanders Research Institute for Agriculture, Fisheries and Food (ILVO)
5	Pestizid Aktions-Netzwerk e.V. (PAN Germany)
6	United States of America — Department of Health & Human Services
7	AnimalHealthEurope
8	European Group for Generic Veterinary Products (EGGVP)

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1. General comments — overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	Health Care Without Harm (HCWH) Europe welcomes the opportunity to comment on the draft 'Reflection paper on antimicrobial resistance in the environment: Considerations for current and future risk assessment of veterinary medicinal products'. We are glad that the European Medicines Agency is launching a reflection process to address the development and spread of antimicrobial resistance (AMR) in the environment as this area has often been overlooked in the past. We believe however that requirements must be included within Marketing Authorisation Applications for Veterinary Medicinal Products to assess the risk of AMR development in the environment. Whilst we concur with the scientific findings outlined, the reflection paper falls short in developing a clear and timed strategy to overcome the identified hurdles and therefore does not address the urgency of the issue. AMR kills an estimated 700,000 people a year worldwide. By 2050, it could kill up to 10 million people annually, making it a major cause of death. As a driver of AMR, pharmaceutical pollution from veterinary sources must be addressed through definitive action. We call on the Committee for Medicinal Products for Veterinary Use to be more ambitious in its reflection paper so that it leads to concrete measures to better monitor and consequently address the link between Veterinary Medicinal Products and AMR.	Partially agreed. Thank you for your comments. The EMA/CVMP understand that you wish for clear timelines for measures against the spreading of AMR. In this context, the EMA/CVMP wish to highlight that this reflection paper is just a first investigation of data gaps and potential measures.

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	We also encourage the European Medicines Agency to develop a similar reflection process for Human Medicinal Products that were not considered in the scope of this paper.	
3	FVE welcomes the EMA proposal to look into the potential impact(s) on ecosystems, animal and human health from the presence of antimicrobial residues (ARs) and/or antimicrobial resistance genes (ARGs) in the environment resulting from the use of veterinary medicinal products (VMPs). While we fully agree with the conclusions that "significant gaps in our knowledge around the specific mechanisms and pathways of AMR" and that "it is not considered appropriate or possible to recommend an update of the current process of Marketing Authorisation Applications (for VMPs), to evaluate AMR in the environment", we note that the draft misses a true 'One Health' approach. It lacks to identify all sources of antimicrobials that may present a risk for the environment and consequently to debate effective mitigation measures. Antimicrobials are used not only in food producing animals, but additionally in humans, companion animals, plants, and other materials. Therefore, a true One Health approach should consider overall uses as well as their interfaces. Even if we accept that in most EU countries, the volumes of antibiotics given to food producing animals far exceed the volumes used in companion animal medicine, this last category should not be forgotten. The draft also mostly focuses on the risk to soil and water via manure, while other mechanisms could be equally important for the	Partially agreed. Thank you for your support and comments. You indicate that the use of antimicrobials in companion animals, humans and for plant protection is insufficiently addressed. As this paper examined the key sources, not all sources of antimicrobials have been addressed. Nevertheless, please note that, in figure 1 in chapter 6 of the paper, plants are mentioned as well as agricultural use in the text above the figure. And so is the use for humans. The use in companion animals might indeed be under-addressed and is now also added to figure 1 and the connected text. This paper mainly focuses on food-producing animals, as for these, as you indicate, the highest quantities of antimicrobials are used and as such they constitute the key source of antimicrobials within the VMP framework. The focus of the reflection paper is on what can be done within CVMP's remit, acknowledging that there are many more stressors. Inappropriate disposal of unused VMPs and packaging after use is indeed not addressed in the paper. This was because

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	environment. Inappropriate disposal of unused or expired products and/or empty containers, possible emission from manufacturing sites (recognising the standards in EU are very high), etc can also be important source. Therefore, both emissions, excretions and disposal should be considered within this concept. Consequently, mitigation measures should be debated, such as by highlighting the need for development and implementation of best practices and guidelines for correct and safe disposal of products. Guidelines on disposal of veterinary antimicrobials, and their containers as well as on handling of animal excretions should be part of the leaflet information as they ensure the responsible use of veterinary antimicrobials by the end users. Finally, more research is necessary to identify the most important sources of manufacturing/use/disposal of medicines having an impact on the environment and the knowledge gaps. Such investigation should look into impacts on humans, animals and the environment from all kind of uses, i.e. human consumption, animal consumption and application on plants/environment. That will allow us to get a clearer picture of the situation, identify interactions and critical control points and propose more proper mitigation measures. FVE therefore recommends to revise the paper to include a more holistic real One Health approach to the paper and to take into consideration the above recommendations.	these are not considered a key source. Nevertheless, it is now addressed in the introduction and chapter 10. Please note that according to the new veterinary regulation, member states are required to have systems for collection and disposal of waste of veterinary medicinal products. Please note that the main risk management measurements currently available are already given in the RONAFA paper (EMA/EFSA, 2017) and it is advised to implement these as far as possible. For further measurements, first the data gaps should be filled in order to be able to identify where and which measures would be required. Please note that this paper has been written from the perspective of the VMP framework and it addresses the issues related to this framework. Writing a paper covering multiple frameworks is not the current scope of this paper and outside the mandate of the CVMP.
4	I greatly appreciate the reflection paper on the risk of AMR in the environment. I would recommend to include some recent and to my opinion crucial scientific articles or studies on the topic of AMR spreading in	Thank you for your support. Not agreed. Thank you for providing the EMA/CVMP with additional references. Please note that review papers are

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	the environment through manure. Many of the cited references in the current version of the reflection paper are excellent opinion papers or reviews which rightfully address the need to consider the risk of AMR in the environment, but it would be very helpful to include more references which show also recent actual data in European countries. Recent references which show data for pig manure in Flanders (Belgium) are: 1/ T. Van den Meersche, E. Van Pamel, C. Van Poucke, L. Herman, M. Heyndrickx, G. Rasschaert en E. Daeseleire. 2016. Development, validation and application of an ultra high performance liquid chromatographic-tandem mass spectrometric method for the simultaneous detection and quantification of five different classes of veterinary antibiotics in swine manure. Journal of Chromatography A 1429: 248-257. 2/ T. Van den Meersche, G. Rasschaert, F. Haesebrouck, E. Van Coillie, L. Herman, S. Van Weyenberg, E. Daeseleire and M. Heyndrickx. 2019. Presence and fate of antibiotic residues, antibiotic resistance genes and zoonotic bacteria during biological swine manure treatment. Ecotoxicology and Environmental Safety, 175: 29-38. 3/ PhD of Tina Van den Meersche: Presence and fate of antibiotic residues, antibiotic resistance genes and zoonotic bacteria in (biologically treated) swine manure and soil. Ghent University (Belgium), 2019. http://hdl.handle.net/1854/LU-8606378 For the above mentioned PhD (which is not publically available), I attach here a relevant selection of the summary:	used, as they combine the results of multiple papers. Furthermore, the publication from 2019 you indicate was published after completion of this paper. Although they confirm the statements made in the reflection paper, The EMA/CVMP considers it currently not necessary to include these in the paper.

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	A longitudinal screening on the presence and fate of selected antibiotic residues, antibiotic resistance genes and zoonotic bacteria in soils fertilized with swine manure was carried out. Therefore, five arable lands were sampled in Flanders at five consecutive time points starting prior to fertilization up until harvest. Soil samples were taken before fertilization, the day of fertilization, after one month, after two months and after harvest. The day of fertilization, a manure sample used to fertilize the arable land under study was taken from the manure tank. The first arable land was fertilized with swine manure from animals with no history of antibiotic administration. On the other arable lands, the swine manure contained at least one of the selected antibiotics. The method developed was used to analyze the manure samples collected the day of fertilization. With regard to the soil samples, minor modifications of the previously validated method were required. Additionally, a selection of the resistance genes to be studied was carried out. Resistance genes associated with the most used antibiotics in Belgian pig production and with animal fecal matter were selected from the literature. The most common tetracycline resistance genes were genes encoding for ribosomal protection proteins (*tet*(M), *tet*(O), *tet*(Q) and *tet*(W)) and genes encoding efflux pumps (*tet*(B) and *tet*(L)). With regard to the macrolide resistance genes, *erm*(B) and *erm*(F) were the most abundant ones and *sul2* was the predominant sulfonamide resistance gene in swine manure. Finally, *bla*TEM, *bla*SHV, *bla*OXA and *bla*CTX-M were resistance genes which confer resistance to β-lactam antibiotics and were associated with swine production. For all of these resistance genes, qPCR protocols from literature were tested. With the exception of the β-lactamases,	

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	all of these selected resistance genes could be quantified by qPCR. In addition, the 16S rRNA gene was used to normalize antibiotic resistance gene levels to total bacteria within each sample for comparative analysis. The results showed that high concentrations of antibiotic residues could be present in the swine manure. In addition, lower concentrations of antibiotic residues could be present in soils up until harvest. This indicated that mobile antibiotics such as sulfadiazine may reach surface and ground water systems and even the drinking water supply if they were not degraded during water treatment. On the other hand, less mobile antibiotics such as doxycycline will sorb to the soil and may have direct and indirect effects on the environment. Extrapolation of these results to other antibiotics and soil types is difficult due to the fact that antibiotics are ionizable and may be present in the soil environment with a positive, a negative or a neutral charge or as zwitterions depending on the pH of the soil. The relative abundances of the selected antibiotic resistance genes in manure were similar for the pigs which were administered antibiotics as for the ones which received no antibiotics. Although the antibiotic resistance genes studied were already present in the soil environment prior to fertilization, an increase in the relative abundances of most of the antibiotic resistance genes studied was observed immediately after fertilization. This increase was followed by a gradual decline to background levels over time. The presence of resistance determinants in manure-borne bacteria which may not survive for extended periods of time in the soil environment and the temporary enrichment of some soil bacteria carrying antibiotic resistance genes due to the addition of nutrients upon fertilization may explain this transient increase in resistance. In addition, no apparent differences	

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	in relative abundances of antibiotic resistance genes in soils were observed between those fertilized with manure with or without antibiotic residues. These results might indicate that the input of resistance genes through fertilization with manure is more important with regard to dissemination of resistance than the selective pressure exerted by the antibiotic residues present in the manure.	
5	Pharmaceuticals as antibiotics are a major achievement of medicine history. Besides their use in human medicine, in the sense of responsibility towards animals held for livestock production, they are needed to cure bacterial infections and reduce sorrow and pain caused by these illnesses. However, those high active substances are likely to be released into the environment. They do not only affect ecosystems and cause environmental problems as pollutants but also contribute to the global burden of antimicrobial resistance (AMR) development. UN Environment identified growing AMR linked to discharge of drugs into the environment as "one of the most worrying health threats today". (UN Environment, December 2017, Antimicrobial resistance from environmental pollution among biggest emerging health threats, www.unenvironment.org/news-and-stories/press-release/antimicrobialresistance-environmental-pollution-among-biggest). PAN Germany shares the concern, that current guidelines on the environmental risk assessment (ERA) of veterinary medicinal products (VMPs) for use in the European Union do not address how to assess the impact of antimicrobials, as veterinary pharmaceuticals, on the prevalence of AMR in the receiving environment.	Thank you for your support.

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	In this regard we agree on the difficulties of predicting fate and effects of AMR in the environment from veterinary use. Thus, conventional quantitative risk assessment is not an appropriate approach to protect the environment from such hazards. Thus, we agree that there is a need for further research but also for research on non-chemical approaches for pathogen and parasite control to reduce reliance on medicinal treatments and to face growing problems with resistance in the first place. It is proven that animal health can be positively influenced by a higher level of animal welfare. Therefore, research is needed on how to improve and promote breeding and husbandry practices that foster animal health and require marginal antimicrobial agents. Every success in reducing the use of antimicrobials will not only contribute to mitigate the problem of AMR but will also contribute to enhance the protection of the environment from pharmaceutical pollution.	
6	We commend the authors on a very nicely done paper on a very challenging issue. The complexities of environmental research and difficulties in predicting outcomes are well discussed. Perhaps the major finding of the manuscript is the pointing out of gaps in knowledge. These include the fact that we have little information on 1) the contribution of veterinary or other antimicrobial drug uses to the total load of antimicrobial resistance (AMR) in the environment, 2) the impacts of (1) on human health, and 3) how to study (1) and (2). The paper describes the serious gaps in knowledge, but still concludes with worst case scenario extrapolation in many non-	Partially agreed. Thank you for your support, an amendment has been made to the conclusions chapter to stress the current uncertainties. Please note that review papers have been cited, as they combine the results of multiple papers. This is considered a more efficient way to cover many years of research.

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	primary research publications to suggest that environmental AMR is a prominent risk driven by agricultural antimicrobial uses. One concern is that most of the citations are review articles or perspective papers and many of the cited publications are in vitro or generally artificial studies. We agree with lines 727-728 and 856-860, that most of the existing "evidence" is extrapolation and conjecture in review articles and there is a lack of primary empirical evidence from in vivo studies. We suggest that the same sentiment be expressed in the conclusions (starting on line 996) for consistency and that primary research articles be cited.	
7	AnimalhealthEurope welcomes the opportunity to comment on this well written reflection paper that considers the current state of scientific knowledge. We acknowledge and appreciate the effort the interdisciplinary team took in drafting this paper. We are in broad support of the overall conclusion of the paper, but have some minor comments in the following section.	Thank you for your support.
8	Many thanks to CVMP/ERAWP/AWP for addressing in this paper the development of antimicrobial resistance in the environment, with considerations for current and future risk assessment of veterinary medicinal products. EGGVP's main comment and concern is that, while the paper includes several references to the "One Health" concept, and in particular the conclusions section concludes that only under a "One Health" approach it shall be possible to minimise environmental contamination with ARs and ARB/Gs, a truly integral focus (covering the impact in ecosystems coming from the use of antimicrobials in humans, animals and plants) is missing.	Partially agreed. Thank you for your support and comments. Please note that this paper has been written from the perspective of the VMP framework and it addresses the issues related to this framework. Writing a paper covering multiple frameworks is not the current scope of this paper and outside the mandate of the CVMP.

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	In order to reach the objective of addressing AMR in the environment, EGGVP's suggests the paper is thoroughly reviewed under a more interdisciplinary angle considering all sources, so that effective mitigation measures can be put in place. In EGGVP's view the paper addresses correctly the limitations and knowledge gaps, and in particular the provisions under the section Conclusions seem to be very realistic and well exposed, with a view on further research and monitoring that may involve different risk assessment and management procedures in the future.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
55–1064	3	Comment: Please consider major revision of this draft by incorporating all above comments throughout all the chapters.	Your comments are addressed where appropriate.
57–58	6	Comment: Authors state that they are focused on impacts of AMR on ecosystem/animal/human health specifically from residues of veterinary medicinal products, or AMR genes. While it is clear that the presence of VMP residues can be linked to VMP use, it is not possible to assume the same direct relationship between drug use and ARGs. This is a critical point, as there is an overwhelming body of evidence that ARGs are ubiquitous in animal guts and in the environment, regardless of whether or not VMPs are used. Proposed change: Suggest adding to the end of the sentence a statement such as, "…taking into consideration that antimicrobial use is not the only contributor to presence of AMR genes in the environment".	Partially agreed. Thank you for your suggestion. Please note that other drivers of AMR are mentioned in lines 77–79 of the executive summary. Your suggested addition is now added to that section.
58	6	Comment: It is important to define the term "environment" for the purposes of this paper. There is a difference between the animal itself, the agroecosystem or	Agreed. It is agreed that the term "environment" can be confusing in some occasions. As the paper is written under the framework of EU Directive 2001/82/EC, the same scope for

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		healthcare or wastewater, surface water or soil environment.	"environment" is used as in the directive. This has been added to the text.
59	6	Comment: The authors define AMR as a phenotype (ability of the microorganisms to become increasingly resistant to antimicrobial to which they were previously susceptible), but lacking is a clear definition of antimicrobial resistance genes (ARGs), or an acknowledgment that genotype is not the same as phenotype. Since the ARGs are a large focus of this work, and are critical to how the authors are defining risk, a definition should be part of this executive summary. Also desirable would be a clear definition of the authors working framework for the relationship between drug, bacterial phenotype, and ARG genotype.	Agreed. Thank you for your comment. The following definition for ARGs has been added to the text: "DNA region within the microbial genome that encodes for reduced sensitivity against specific antimicrobials" This should also express the relationship mentioned in your comment.
74–75	5	Comment: As well as in humans and animals natural selection of microbials takes place in the environment too. This natural process causing the development of AMR is driven by many influencing factors including the presence of antimicrobials. Proposed change: However, it is acknowledged that VMPs that are antimicrobial in nature act similarly to their human medicine counterparts and that many other pressures~~,~~	Agreed. Thank you for your suggested change, it has been applied in the text.

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		~~including natural selection,~~ drive the development of environmental AMR by natural selection.	
79	6	Comment: By limiting the analysis to "ARGs excreted from animals treated with VMPs", authors are implying that there is a difference between the ARGs excreted from animals treated with VMPs, and the ARGs excreted from untreated animals. They are equating "treatment" with "presence of ARG". This is a dangerous oversight, as it excludes all inputs from most wildlife and organically raised animals, and confounds conclusions about impacts of veterinary drug use. Potentially underestimating the risk from the environment.	Agreed. Thank you for your comment. The text has been amended accordingly.
84–87	6	Comment: The 2012 Forsberg Science paper "The Shared Antibiotic Resistome of Soil Bacteria and Human pathogens, presents strong evidence that the soil is the original source of antibiotic resistance in human clinical pathogens. This work was supported by the 2013 Wellington Lancet ID paper "The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria". And 2013 Finley CID paper "The Scourge of Antibiotic Resistance: The Important Role of the Environment", among others. Thus, it seems improper to state that the role of naturally present environmental bacteria is	Agreed. Thank you for your comments. Amendments have been made citing the suggested references.

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		unknown, or that their relevance to human is unknown.	
84–87	6	Comment: It is accepted that bacteria can be transported between different compartments through the environment. Since AMR will be present wherever bacteria are present it is not contested that AMR will move through the environment. What is undefined is how much each VMP application contributes and the specific health relevance of each VMP application.	Agreed. Thank you for your comments. Amendments have been made in this section.
88–93	6	Comment: Similarly, it is accepted that mobile genetic elements (MGEs) are present in any bacterial habitat and they transfer. The same lack of specific knowledge also exists. Proposed change: Are there any specific references for this comment? If so cite them: There is evidence that AMR pathogens have developed through these pathways and have impacted on human and animal wellbeing.	Partially agreed. Thank you for your comments. Amendments have been made in this section.
89–90	6	Comment: This example of the environment as a bridge is incomplete – it does not mention human -to – biosolid – to environment – to animal.	Agreed. Thank you for your comments. Amendments have been made in this section.

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		Proposed change: Could edit to either "…compartments; e.g. animal manure to…" or it could work by stating wastes or manure/biosolids "compartments; e.g. manure/biosolids to …".	
92–93	6	Comment: No specific studies are cited that describe the pathways. Proposed change: Cite specific studies to improve credibility of the statement.	Agreed. A reference has been added to the text.
99–109	2	Comment: HCWH Europe rejects the idea that it is not considered appropriate or possible to update the current Marketing Authorisation Applications process to assess the risk of AMR development in the environment for Veterinary Medicinal Products. (i) Despite a significant fall in the sales of antibiotics for use in animals in Europe between 2011-2015, the volume of antimicrobials sold for veterinary use is still greater than for human use. We can therefore expect the contribution from veterinary medicines to environmental AMR to be significant. (ii) While we can deplore the lack of data, scientific research has demonstrated that Veterinary Medicinal	The EMA/CVMP would like to thank the HCWH Europe for their comments and their interest in this reflection paper. The objective of this reflection paper is to identify the current state of knowledge and the corresponding level of uncertainty in order to allow for additional guidance for regulatory environmental risk assessment (ERA) of veterinary medicinal products. It should be noted that the amount of AM for the RQ calculation is already considered in the current ERA. However, with respect to the several gaps of knowledge as identified in the document, it was considered not feasible at this stage to provide clear instructions how to standardise the assessment and which studies should be conducted to address the specific risk of AMR to the environment.

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		Products have a negative impact on environmental and animal health, e.g. the near extinction of vultures feeding on animals treated with diclofenac in Pakistan.	
109–113	5	Comment: We agree on the importance of the implementation of education and training programmes for farmers and practitioners to limit the emergence, spread or development of AMR at the farm level. However, such education should not be limited to best practices on disposal of manure, but needs to be complemented by best practice measures on enhancing animal welfare to pare the need for antibiotics down in the first place. Training and information should include the knowledge on preventive measures that foster animal health on different levels (breeding practice, husbandry practice, livestock facilities (pigsty, cowshed, …), integrated concepts of hygiene, etc.). Proposed change: Possible risk mitigation measures to reduce the incidence of AMR in the environment are identified. These measures tend to involve the implementation of best practices on disposal of manure as well as best practices on enhancing animal welfare and the implementation of education and training programmes for farmers and practitioners. Implementation of best practices on disposal of manure as well as on enhancing animal welfare may help limit the	Partially agreed. Thank you for your comment. The EMA/CVMP agrees that improved animal welfare potentially reduces potential microbial infection and in the scope of this paper the text should specifically refer to the goal to reduce microbial infections. The text has been amended accordingly.

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		emergence, spread or development of AMR at the farm level.	
110–114	3	Comment: Correct disposal of expired, unused medicines or left-overs is equally important. Include recommendation. Proposed change: Add as additional risk mitigation measures setting up systems to correctly dispose medicines and guidelines for correct disposal.	Agreed. Thank you for your comments. Amendments have been made in this section including suggestions on proper disposal.
111–112	2	Comment: HCWH Europe suggests to include the promotion of sustainable farming conditions as an efficient risk mitigation measure as antimicrobial use in animal husbandry is often required by intensive farming practices.	Agreed. Thank you for your comments. Amendments have been made in this section including suggestions to improve animal welfare to reduce the risk of infections.
122–123	6	Comment: There is no dispute that the environment is involved in AMR. How much, where, and when for priority AMRs are the questions.	Agreed. Thank you for your comment, this is addressed in section 9.2
152–154	6	Comment: The term One Health is used to describe a principle which acknowledges that human, animal and ENVIRONMENTAL health are interconnected. Additionally, rather than say AMR is an issue that	Agreed. Thank you for your comment, the text has been adapted.

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		must be "tackled in both" – it is more accurate to frame the issue as one which requires a systems-based approach that considers all three pillars of One Health – human, animal and environmental. Proposed change: Add the term environmental. Change "tackled in both" to say that it requires a systems approach that considers all three pillars of One Health – human, animal and environmental.	
154–155	6	Comment: Citing the Calistri 2013 paper with the "four key elements for one health" appears odd – the paper is not well cited – so it appears to be an odd choice as background for the One Health concept. Proposed change: Suggest re-writing this paragraph as it seems an odd representation of the spirit of the One Health concept and intention.	Agreed. Thank you for your comment. Citing review papers/chapters indeed adds little to the original source. The text has been amended accordingly.
159	3	Comment: With the estimated number of companion animals to be about 290 million in Europe alone, we should not exclude them from the One Health approach, especially since those animals are in direct contact with humans and their immediate environment.	Partially agreed. Thank you for your comment. This paper mainly focuses on food-producing animals, as for these the highest quantities of antimicrobials are used and as such they are the key source of antimicrobials in the environment within the VMP framework. Nevertheless, the use in companion animals might indeed be under-addressed and is now also added to

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		Proposed change: Adapt the whole draft to reflect this.	figure 1 and the connected text. Direct human health risks due to contact with companion animals are outside the scope of this reflection paper.
160	6	Comment: One Health does encompass the environment by definition. The authors do not provide evidence for the statement that the environment is "a significant link between humans and animals" as regards AMR. Instead, the authors lay out the reasons in lines 101-108 that that statement is incorrect. Proposed change: Suggest removing the statement. Or modify to say "more research is needed to understand the risk and/or link between the environment and AMR in humans and animals".	Agreed. Thank you for your comment. The text has been amended accordingly.
167–169	6	Comment: "Use of antimicrobials in humans, animals (including in aquaculture) and plants leads to contamination of the environment both with antimicrobials and resistant bacteria." In regard to resistant bacteria, the statement is not always accurate. For example, Vikram et al. Appl Environ Microbiol (2017) 83:e01682-17 demonstrated that cattle produced without using antibiotics shed AMR (ARB and ARGs) as similar levels to cattle produced using antibiotics.	Partially agreed. Thank you for your comment. It does however address cited text which should not be adapted. The new information is added to the section below the citation.

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		Proposed change: Suggest deleting lines 164-173 or following up with a clarifying statement such as, "There are conflicting studies regarding AMR development in the environment with data gaps requiring further research". If there is data showing use of antimicrobial drugs on crops results in environmental AMR, those studies should be quoted to lend scientific credibility to the statement.	
172–173	6	Comment: But the contributions of human waste effluents must also be considered using the same methods. If all efforts are only directed at one source without regard to other sources such as human effluent, mitigation efforts will not be successful, if the source is human effluent from hospitals, for example. Proposed change: Add "human" to read: "…given to the contribution of veterinary antimicrobial use to the environmental resistome in addition to other sources."	Not agreed. Thank you for your comment. It does however address cited text which should not be adapted. Also, this reflection paper highlights the potentials within the VMP framework to contribute to this multifactorial issue.
188–191	2	Comment: The Committee for Medicinal Products for Veterinary Use lists hurdles to analyse AMR trends from environmental sources, but fails to identify solutions	Not agreed. Thank you for your comment. We wish to highlight that this reflection paper is just a first investigation of data gaps and potential measures.

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		to overcome these issues within a clear time framework. HCWH Europe believes that the reflection paper should go beyond describing the problems and offer pathways to resolve them.	
190–191	6	Comment: Does "standardised requirements" refer to the need for the data to establish the risk that is associated with finding a bacterium with AR and that resistance being spread to a pathogen that infects a human? Another reason that trends can't be analysed is because we don't understand the background levels of AMR in the wider environment, regardless of presence of anthropogenic influences. Non-impacted environments have AMR. Proposed change: Suggest change to: Currently, it is not possible to analyse trends in AMR from environmental sources over time due to the absence of standardised or routine monitoring systems due to: LACK OF DATA TO IDENTIFY safe thresholds for antimicrobials in the environment (in terms of impact on AMR), NEED FOR RESEARCH TO UNDERSTAND THE RISK OF AMR TRANSMISSION FROM A GIVEN ENVIORNMENT TO A PATHOGEN THAT CAUSES INFECTION(IE Impact of AR bacterium on human and animal health) AND DIFFICULTY IN STANDARDISING methods ACROSS DIVERSE ENVIRONMENTS for ISOLATING AND	Not agreed. Thank you for your comments. We have not applied the changes suggested as these already identify the knowledge gaps discussed in section 9.2

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		susceptibility testing of bacteria from soil samples (IE LACK OF ECOLOGICALLY RELEVANT CUTOFFS FOR MOST ENVIORNMENTAL BACTERIA).	
194	6	Comment: "Unnecessary antimicrobial use" must be specifically defined as this is interpreted differently by each audience.	Agreed. Thank you for your comment. This quote originates from the reference of O'Neill (2016) as cited in the paper. It refers to use not related to animal welfare and food security. Infection prevention and growth promotors are given as example. This information is added to the text.
195–197	5	Comment: PAN Germany very much welcomes the recommendation for a systematic monitoring of waste products from antibiotic manufacturing by pharmaceutical companies and to support the installation of effective waste processing facilities to reduce or eliminate Active Pharmaceutical Ingredients (APIs) from being discharged into the environment. Since most of the manufacturing industry of pharmaceuticals is located in southeast Asia, we see the urgent need for expanding the regulatory framework for Good Manufacturing Practice (GMP) to include compulsory environmental criteria. (PAN Germany, joint letter of concern, 2019 https://pan-germany.org/download/joint-letter-in-reaction-to-the-strategic-approach-on-pharmaceuticals-in-the-environment/).	Agreed. Thank you for your comment. In addition to the suggestion derived from the O'Neill (2016) review, the text will be expanded with "This line of action could for example be considered within the regulatory framework for Good Manufacturing Practice (GMP) to include compulsory environmental criteria."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Although out of the direct scope of this paper, it is noted that this review also recommends pharmaceutical companies to establish a systematic monitoring of waste products from their antibiotic manufacturing processes, and to support the installation of effective waste processing facilities to reduce or eliminate Active Pharmaceutical Ingredients (APIs) from being discharged into the environment. Moreover, it is recommended to expand the regulatory framework for Good Manufacturing Practice (GMP) to include compulsory environmental criteria.	
210	7	Comment: Antimicrobial resistance is abbreviated as 'AR' here. However, this is the abbreviation for *antimicrobial residues* in this reflection paper. 'AMR' should be used as abbreviation instead. Proposed change: Antimicrobial resistance (~~AR~~ AMR) is the ability of a microorganism to survive […].	Agreed. The comment is appreciated. The abbreviation has been revised accordingly.
220–222	4	Comment: According to my knowledge, integrons are not mobile in themselves; they can however be located in a mobile element such as a transposon or a conjugative plasmid.	Agreed. The comment is appreciated. The wording has been revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The recruitment of MGEs such as conjugative plasmids, transposons, ~~integrons~~, insertion sequences, and integrative conjugative elements, including the integrons or genes they carry, will also occur.	
224–225	6	Comment: This statement could be strengthened if using a citation of a scientific study rather than a review article and citations that are more comprehensive rather than just referencing food animals, "Food Animals and Antimicrobials: Impacts on Human Health". First, this citation implies that "AMR development" is predominately due to antimicrobial use during food animal production. The relative contributions of medical, veterinary, and manufacturing applications of antimicrobials to "AMR development" has never been demonstrated empirically. Second, "AMR development" needs to be specifically defined. There is little to no evidence (outside of *in vitro* or short-term inoculation studies) that antimicrobial use in food animals lead to sustained (more than 30 days after cessation of treatment) increases in AMR levels. Proposed change: Delete the sentence.	The EMA/CVMP would like to thank the United States of America — Department of Health & Human Services for their valuable comments and the interest raised for this document. The EMA/CVMP acknowledges that primary research is the pillar of science and that preferentially primary research articles should be cited. As kindly suggested, several statements will be strengthened or balanced with primary research articles when needed. However, the EMA/CVMP considers that high-level reviews published in peer-reviewed journals are also of importance to consider. Numerous primary research papers are also included in the core part of the document. Concerning the particular sentence highlighted, it does not imply that it is the use of AM in food-producing animals, but AM use at a more general scale either in human or veterinary medicine. However, to gain clarity, it was accepted to revise the paragraph as suggested with minor changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
228–235	6	Comment: These statements are only supported by review articles. This cites another review article. The statements would be better supported if articles that described an antimicrobial application in food-animal production "selecting" for a resistant pathogen that caused casualties could be cited. Proposed change: Generalized concerns exist that antimicrobial use selects for resistant bacteria (ie. increase abundance of a sub-population of a resistant bacterial taxon relative to the total abundance of the taxon) which may have a deleterious impact either as a pathogen itself or by HGT of antibiotic resistance gene(s) to a pathogen.	Partly agreed. The EMA/CVMP would like to thank the United States of America – Department of Health & Human Services for their valuable comments and the interest raised for this document. We acknowledge that primary research is the pillar of science and that preferentially primary research articles should be cited. As kindly suggested, several statements will be strengthened or balanced with primary research articles when needed. However, the EMA/CVMP considers that high-level reviews published in peer-reviewed journal are also of importance to consider. Numerous primary research papers are also included in the core part of the document. Concerning the particular sentence highlighted, it does not imply that it is the use of AM in food-producing animals, but AM use at a more general scale either in human or veterinary medicine. However, to gain clarity it was accepted to revise the paragraph as suggested with minor changes.
231	6	Comment: Review articles (Alekshun and Levy; Davies and Davies) are quoted rather than scientific studies. Proposed change: Cite empirical, primary research scientific studies, not just review articles.	Partly agreed. Section 4 of the reflection paper describes general concepts of antimicrobial resistance. Those concepts are considered well known. That’s why high-level peer-reviewed papers are cited here. The EMA/CVMP acknowledges that primary research is the pillar of science and that preferentially primary research articles should be cited. As kindly suggested, several

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			statements will be strengthened or balanced with primary research articles when needed. However, the EMA/CVMP considers that high-level reviews published in peer-reviewed journal are also of importance to consider. Numerous primary research papers are also included in the core part of the document.
238–240	6	Comment: Again, a review article (no empirical data) is cited in support of a vague theory that release of AMR and ARGs leads to an increased recruitment of MGEs, presumably the MGEs harbour ARGs and are recruited by pathogens. As written the paragraph suggests that antimicrobial use in food-animal production increases the amount of ARG harbouring MGEs in the environment and their recruitment into pathogens without citation of primary research. Proposed change: This paragraph should either be removed or primary research on ARGs, MGEs, and pathogens in the environment must be cited.	Partly agreed. Section 4 of the reflection paper describes general concepts of antimicrobial resistance. Those concepts are considered well known. That's why high-level peer-reviewed paper are cited here. The EMA/CVMP acknowledges that primary research is the pillar of science and that preferentially primary research articles should be cited. As kindly suggested, several statements will be strengthened or balanced with primary research articles when needed. However, the EMA/CVMP consider that high-level reviews published in peer-reviewed journal are also of importance to consider. Numerous primary research papers are also included in the core part of the document.
242–243	4	Comment: Coss resistance is not a bypass of same but of different antimicrobial targets via the same resistance determinant. Proposed change:	Agreed. For clarity, definition for cross- and co-resistance have replaced the text between brackets.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Bpass of ~~same~~ **different** antimicrobial targets via the same resistance determinant.	
247–251	6	Comment: Yes, co-resistance exists. However, risk assessments should not assume that the genetic linkage of ARGs results in co-selection. See Appl. Environ. Microbiol. 82:7197 (2016) for an example of when co-selection did not occur. Proposed change: Add the statement, "Risk assessments should not assume that genetic linkage of antimicrobial resistance genes results in co-selection and cite Appl. Environ. Microbiol. 82:7197 (2016).	Not agreed. It is acknowledged that the environment has an international dimension, notably concerning sites of production etc., but it was decided to narrow the scope of this document to the EU situation. Thus, it was decided to collect and quote only studies representative for the European geographic area in order to specifically address current European practices of antimicrobial use. However, as kindly suggested, several statements will be balanced with primary research articles when needed.
255–258	7	Comment: The latest report was published in October 2018. (Please also amend the reference in the bibliography.) Proposed change: The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, set up by the European Medicines Agency (EMA) following a request from the European Commission, publishes an annual report on sales of veterinary antibiotic active ingredients in EU/EEA countries. <u>The latest report, published in October 2018, shows that sales of antibiotics for use in animals in Europe fell by 20%</u>	Agreed. Thank you for the information. We have updated the text with the most recent version of the surveillance report.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		between 2011 and 2016. This covers 25 countries that provided data for this period~~. (30 countries reported data for 2015, 25 of which provided data for the full 5-year period that the report covered 256 (EMA/ESVAC, 2017)). The most recent report, published in October 2017, showed that sales of antibiotics for use in animals in Europe fell by 13.4% between 2011 and 2015~~ (EMA/ESVAC, ~~2017~~*2018*). It…	
283 through to end of the document	7	Comment: Please do not use the term "emissions" when excretion of veterinary pharmaceuticals by animals is meant. There is specific legislation around industrial emissions that can conflict with the needs of our industry. Please use "emissions" only in connection to inanimate sources. Proposed change: Please use the term "*excretion*" for the purpose of environmental risk assessments for VMPs.	Not agreed. The term emission is used only a limited number of times in the paper. Only in the beginning of section 6.1, emission only as excretion is meant, but this is explained in the same sentence. No changes have therefore been made.
287	3	Comment: Change "emissions" to "animal excretions and disposal VMPs". Please align the whole text though. Proposed change (if any): Change "emissions" to "animal excretions and disposal VMPs".	Not agreed. Thank you for your comment. Please note that the EMA/CVMP has not used the term excretion as VMPs may also be secreted from animals or emitted from manure storage for example.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
292	3	Comment: Humans use is both therapeutic and preventative! Animal use should also include companion animals. Proposed change (if any): Change the figure to note human use and animal &plant use; to include companion animal in the picture.	Agreed. Thank you for your comment. Figure 1 of chapter 6 has been adapted accordingly.
295–297	6	Comment: This statement is only partially explains antimicrobials released into the environment "As the activity of antimicrobial substances does not necessarily end when the bacterial infection has been treated in the animal, a *widespread selective pressure* on bacteria in the environment may be imposed." The terminology "widespread selective pressure" is not supported by data – in fact there are very limited data to understand the effect of antimicrobial compounds on environmental bacteria. However, the data do suggest that these compounds can be degraded by existing bacteria and/or environmental conditions (light, temperature) and that the compounds sorb to soil particles making them less available. Therefore the "available dose" is unknown in most cases – since each antimicrobial acts differently once it enters the environment and should be very dependent on the environment (as discussed in the next paragraph). As	Partially agreed. Thank you for your comment. Please note that the term "may" has been used while the term "widespread" has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		a result, more research is warranted to understand the effect of the release of antimicrobial compounds into the environment, but at this time "widespread selective pressure" is inaccurate terminology. Proposed change: Suggest removing sentence or at least the reference to "widespread selective pressure".	
307–313	4	Comment: Although in the context of cross contamination of feed with antibiotics, the study of Peeters et al. (2016) gives some interesting data on the excretion of chlortetracycline and doxycycline and of sulfadiazine-trimethoprim by experimentally dosed pigs with feed containing a 3% carry-over level of these antibiotics. L. E. J. Peeters, E. Daeseleire, M. Devreese, G. Rasschaert, A. Smet, J. Dewulf, M. Heyndrickx, H. Imberechts, F. Haesebrouck, P. Butaye and S. Croubels. 2016. Residues of chlortetracycline, doxycycline and sulfadiazine-trimethoprim in intestinal content and feces of pigs due to cross-contamination of feed. BMC Veterinary Research 2016, 12:209.	Agreed. Thank you for the information, it has been added to the paper.
316–320	6	Comment: While the data on excretion, degradation and transformation may be available, the key data needed – the rate at which a susceptible bacterium becomes	Agreed. Thank you for the information.

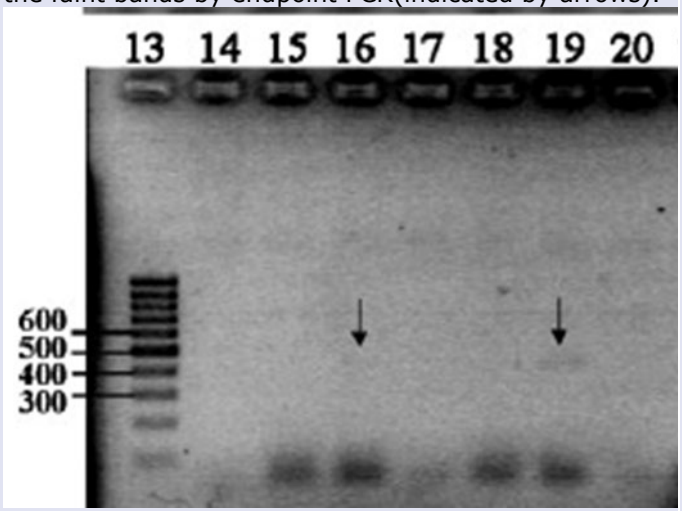
Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		resistant to an antimicrobial that is released into a given environment – is not available to my knowledge. It is important to consider the biological phenomenon as well as the chemical. Additionally it is well known that most bacteria in the environment are not actively growing and the fact that an antibiotic or residue is in the environment, does not mean that selection will occur, particularly without active bacterial growth.	
321	3	Comment: Remove 'routinely' in antimicrobials are also routinely used in aquaculture, … This is incorrect, e.g. Norway, one of the biggest aquaculture producers hardly uses any antimicrobials. Proposed change: Remove 'routinely'	Agreed. Thank you for your comment, the term "routinely" has been removed.
333	4	Comment: In figure 2, from the manure tank to the soil, degradation (also in biogas plant) is mentioned. Besides biogas plants, there are also other manure treatment systems such as the biological removal of nitrogen from swine manure, which is highly used in regions which are Nitrate Vulnerable Zones such as Flanders in Belgium. More details can be found in:	Agreed. Thank you for the information. As suggested, "also in biogas plant" could indeed better be amended to "also in manure treatment systems". However, after some consideration because of other comments, the whole figure has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		T. Van den Meersche, G. Rasschaert, F. Haesebrouck, E. Van Coillie, L. Herman, S. Van Weyenberg, E. Daeseleire and M. Heyndrickx. 2019. Presence and fate of antibiotic residues, antibiotic resistance genes and zoonotic bacteria during biological swine manure treatment. Ecotoxicology and Environmental Safety, 175: 29-38 Also composting is performed of the solid fraction of swine manure: Kim, K.R., Owens, G., Ok, Y.S., Park, W.K., Lee, D.B., Kwon, S.I., 2012. Decline in extractable antibiotics in manure-based composts during composting. Waste Manag. 32, 110–116. Selvam, A., Xu, D., Zhao, Z., Wong, J.W.C., 2012a. Fate of tetracycline, sulfonamide and fluoroquinolone resistance genes and the changes in bacterial diversity during composting of swine manure. Bioresour. Technol. 126, 383–390.	
333–334	3	Comment: We think Figure 2 is very confusing and missing many aspects. E.g. the term 'veterinary consumption' is incorrect, it should be 'animal consumption'. Why split aquaculture from the other animals? What is the difference between manure and dung? What is 'overflo'? If Figure 2 depicts emissions and fate of antimicrobials in the environment following use of VMPs, how human consumption of VMPs is justified?	Agreed. Thank you for your comment. The EMA/CVMP agrees it is best to delete the figure.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		There are also more problems with the associations and terms used in this scheme. Proposed change: We strongly suggest to delete this figure.	
345–349	5	Comment: PAN Germany agrees on the need for further research on the fate and behaviour of veterinary antimicrobials in the environment. However, equal attention should be given to measures obtaining to reduce the need for antimicrobials in livestock production, which serves the EU precautionary principal.	Not agreed. Thank you for your comment. Please note that this section is on the fate and behaviour of antimicrobials. Reduction of the use of antimicrobials is discussed in chapter 10.
346–364	6	Comment: In order to "assess the role of veterinary use of antimicrobials in the complex biological phenomena of the environmental resistome and mobilome" it is important that the BIOLOGICAL component be considered. Critical consideration of risk analysis – ie of being able to quantify based on bacterium, environment, manure type (source material) the rate of development of resistance in environmental bacteria given the release of a specific pharma compounds/derivative. Which the authors correctly discussed in the second paragraph. Without incorporation of that data, it would not be possible to "assess the role of veterinary use of antimicrobials in the complex biological phenomena of the	Partialy agreed. Thank you for your comment. Please note that this section is on the fate of the antimicrobials, not on their effects. The biological part in the fate would be mainly biodegradation of the ARs. This has been added to the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		environmental resistome and mobilome". However, further research on this topic is warranted as suggested by authors. Proposed change: Later in the paper there is more discussion of the biological piece of risk associated with the occurrence of and AMR in the environment, but some mention of the importance of the biological component is warranted in the introduction to this section.	
379–380	6	Comment: How is it that "Knowledge of the concentrations of ARs in manure is important as it can give an indication as to the maintenance of bacterial resistance in the environment" – that information would require additional research regarding the relationship between AR and development of AMR bacteria to a given antibiotic in a given environment, etc.	Not agreed. Thank you for your comment. Knowledge on concentrations can be used together with new knowledge.
397	4	Comment: In table 2 with concentrations of antibiotics in manure, recent data can be added from Belgium for swine manure as given in Table 3 (Overview of antibiotic residue concentrations (µg/kg) recovered from swine manure samples at different farms or from different manure pits on one farm and antibiotic use	Not agreed. Thank you for the additional information. Please note that the section presents the review as published by Massé et al. (2014). It is not a complete list of all publications of ARs in manure and does therefore not contain any information published after 2014.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		in the respective pens during the three months before sampling) of the following reference: T. Van den Meersche, E. Van Pamel, C. Van Poucke, L. Herman, M. Heyndrickx, G. Rasschaert en E. Daeseleire. 2016. Development, validation and application of an ultra high performance liquid chromatographic-tandem mass spectrometric method for the simultaneous detection and quantification of five different classes of veterinary antibiotics in swine manure. Journal of Chromatography A 1429: 248-257.	
459	2	Comment: The reflection paper gives little attention to manufacturing pollution and its links with environmental AMR. HCWH Europe believes that this aspect should be considered for current and future risk assessment of veterinary medicinal products. To limit potential adverse effects of veterinary medicines on the environment, we call for Environmental Risk Assessments to address the risk associated with API discharges from manufacturing sites, also outside the EU.	Not agreed. Thank you for your comment. As already stated, addressing this risk is outside the scope of this paper.
502–504	6	Comment: Where are the citations for this result? Is this only considering the upper cm of soil?	Agreed. Thank you for your comment. The information comes from two references as cited in Girardi et al. (2011), as referred to at the end of the paragraph.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Samples were taken from the top 2.5 cm as well as from 0–30 cm. The original citations have been added to the text.
507–508	6	Comment: This is a very borderline finding. It should not be cited in a, document of this importance. No confirmation of the faint bands by endpoint PCR(indicated by arrows).  Proposed change: Given the lack of confirmation of the endpoint PCR finding authors should remove citation and/or remove statement.	Partially agreed Thank you for your comment. The reference to this finding has been softened.
509–512	6	Comment:	Not agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Again, the biological component is also important. Without information about the risk or even just the rate of AMR bacteria that result from exposure to AR then these AR data are of limited value. These data, in addition to the quantitative information about the antimicrobial compounds, are critical to "elucidate the role of the environment in the potential transfer of relevant AMR bacteria with associated risks to human and animal health" Proposed change: Add text regarding the need for better understanding of "AMR bacteria of risk to human health".	Thank you for your comment. This section focuses on the fate. Clearly, these kind of data need to be relevant for the associated effect/risk assessment that the comment made refers to. However, that can best be addressed in section 8.
515–562	8	Comment: The chapter focuses on excretion via the GI tract, but excretion via urine should also be considered. Resistant bacteria and resistance genes might be excreted into the environment via urine. Especially in persisting UTI's, frequently caused by MDR E. coli (animal & human origin as well).	Agreed. This chapter focused primarily on the GIT, as the GIT is considered the principal source of excretion for resistant bacteria due to the diversity of the GIT microflora. The EMA/CVMP appreciates the comment and the chapter has been updated to mention that the urinary tract may also be considered as a reservoir of AMR. A reference has been included in consequence.
519–520	6	Comment: Again, all cited documents are review articles rather than scientific publications. Holzbauer and Chiller is a brief book review. Proposed change:	Not agreed. All these reviews are written by recognised scientists in their field of competence. The EMA/CVMP considered those reviews as representing a summary of all the primary research made by the authors.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Recommend deletion of sentence beginning with "As the use…" or cite scientific studies.	
528–531	6	Comment: Baron is inoculated one day old chicks in isolators. Beyer examined swine. D'Costa 2011a and 2011b are the same article which is "Antibiotic resistance is ancient". Martinez 2015 is a review article. Toutain 2016 is a review article. Agga et al Appl Environ Microbiol (2016) 82:7197 and Miller et al Foodborne Pathog Dis (2018) 15:689 demonstrated that in feed chlortetracycline in beef cattle did not increase the reservoir of ARGs or ARB in feces. Vikram et al Appl Environ Microbiol (2017) 83:e01682-17 demonstrated that the ARG and microbiomes in colon contents of cattle produced with and without antibiotic use were very similar. Proposed change: The 2 primary research citations should be contrasted with Schmidt et al Appl Environ Microbiol (2013) 79:2273 that demonstrates that ceftiofur injection in beef does not increase alter the fecal levels of resistant E. coli permanently.	Not agreed. It is acknowledged that the environment has an international dimension, notably concerning sites of production etc., but it was decided to narrow the scope of this document to the EU situation. Thus, it was decided to collect and quote only studies representative for the European geographic area in order to specifically address current European practices of antimicrobial use. However, as kindly suggested, several statements have been balanced with primary research articles when needed.
534	6	Comment: Again, Toutain is a review paper. The specific criteria for "hot spot" designation must be specifically defined and supported by empirical evidence.	As mentioned previously, all these reviews are written by recognised scientists in their field of competence. The EMA/CVMP considers those reviews as representing a summary of all the primary research made by the authors.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Cite scientific literature and provide a definition for the term "hot spot".	
534–537	6	Comment: The sentence could be strengthened for scientific accuracy. Propose change: Fecal bacteria (commensal and pathogenic) harbour a range of ARGs regardless of antibiotic treatment. Studies suggest that environmental impact from AMR in faeces is similar for treated and untreated animals.	Agreed. As kindly suggested, primary research articles have now been included highlighting that non-treated animals also harbour a range of ARGs.
534–537	6	Comment: Bibbal 2007 examined small number of swine for in non-production setting for only 7 days after treatment Proposed change: Fleury et al., 2015 examined inoculated swine. This should be contrasted with the results of Schmidt et al Appl Environ Microbiol (2013) 79:2273 that demonstrates that ceftiofur injection in beef does not increase alter the fecal levels of resistant E. coli permanently.	Partly agreed. It was decided to narrow the scope of this document to the EU situation. Thus, it was decided to collect and quote only studies representative for the European geographic area in order to specifically address current European practices of antimicrobial use. However, as kindly suggested, primary research articles have now been included highlighting that non treated animals also harbour a range of ARGs.
534–537	6	Thames et al., 2012 examined dairy calves. However, 9 ARGs were examined by absolute abundance antibiotic treatment did have a significant impact. By	Partly agreed. It was decided to narrow the scope of this document to the EU situation. Thus, it was decided to collect and quote only

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		relative impact antibiotic treatment increased only 1 ARG. Indeed this reference more strongly demonstrates that ARGS are present at very similar levels in the faeces of untreated animals. Again Vikram et al Appl Environ Microbiol (2017) 83:e01682-17 could be citied since it demonstrated that the ARG and microbiomes in colon contents of cattle produced with and without antibiotic use were very similar.	studies representative for the European geographic area in order to specifically address current European practices of antimicrobial use. However, as kindly suggested, primary research articles have now been included highlighting that non treated animals also harbour a range of ARGs.
549–552	6	Comment: The sentence could be edited for accuracy. Proposed change: This needs to be contrasted with Agga et al Appl Environ Microbiol (2016) 82:7197 and Miller et al Foodborne Pathog Dis (2018) 15:689 demonstrated that in feed chlortetracycline in beef cattle had minimal short term and no longer term impact on ARB and ARG in feces and pen surfaces.	Partly agreed. It was decided to narrow the scope of this document to the EU situation. Thus, it was decided to collect and quote only studies representative for the European geographic area in order to specifically address current European practices of antimicrobial use. However, as kindly suggested, primary research articles have now been included highlighting that non treated animals also harbour a range of ARGs.
557–562	6	Comment: As stated by authors – the spread of manure TEMPORARILY increases AMR in amended soil. The conclusion that "Thus, the use of waste from treated animals for manure spreading contributes to the global dissemination of AMR in the environment (Heuer et al., 2011; Jensen et al., 2002; Sengeløv et al., 2003)" is not supported by the finding of this	Agreed. The EMA/CVMP agrees that the sentence is to affirmative. Thus, the wording has been revised as suggested.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		temporary increase. "Dissemination" is the action of spreading something" The topic of dissemination following manure application requires additional research. Proposed change: Change this statement since the temporary increase in AMR is soil is not yet shown as leading to "global dissemination of AMR in the environment". Perhaps it is correct to state that manure application may contributed to the environmental resistome, however, further research is needed to understand the impact.	
561–562	6	Comment: Again, waste from untreated animals also contains AMR, frequently at levels similar to treated animals. Proposed change: "…use of waste from treated and untreated animals…".	Partly agreed. The wording has been slightly revised and primary research articles have now been included highlighting that non-treated animals also harbour a range of ARGs.
563–615	8	Comment: Considerations about how environmental conditions affect resistance gene selection and transfer among bacteria could be included. The speed of resistance development might be slower in the environment than in the animal/human body,	Agreed. The EMA/CVMP notes the comments. A sentence has been added to underline that further research would be needed for better understanding of the environmental conditions that could influence positively or negatively the spatio-temporal dynamics of selection and dissemination of resistant determinants.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		due to environment's colder temperature and the lack of host.	
568	6	Comment: Heuer is a review article. Proposed change: Cite a scientific study or delete the sentence.	Not agreed. The EMA/CVMP acknowledges that primary research is the pillar of science and that preferentially primary research articles should be cited. As kindly suggested, several statements will be strengthened or balanced with primary research articles when needed. However, the EMA/CVMP considers that high-level reviews published in peer-reviewed journal are also of importance to consider. Numerous primary research papers are also included in the core part of the document.
573–574	6	Comment: Bengtsson-Palme et al and Heuer are both review articles. Proposed change: Cite a scientific study or delete the sentence.	Not agreed. The EMA/CVMP acknowledges that primary research is the pillar of science and that preferentially primary research articles should be cited. As kindly suggested, several statements will be strengthened or balanced with primary research articles when needed. However, the EMA/CVMP considers that high-level reviews published in peer-reviewed journal are also of importance to consider. Numerous primary research papers are also included in the core part of the document.
578–582	6	Comment: None of these articles describe research demonstrating that an ag antibiotic use increased the occurrence of these antimicrobial resistant bacteria. It	Not agreed. The first sentence of the paragraph mentions that "For non-environmental bacteria, survival seems more critical than growth in the environment."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		is also important to state that all these bacteria are important members of the soil microbiome and while some are also members of the animal microbiome, just because they are the same genus and species, does not mean that they will automatically grow and thrive in the environment, when coming from an animal. Proposed change: Delete sentence.	This paragraph is considered sufficiently balanced.
583–586	6	Comment: These are review articles. Proposed change: Cite a scientific study or delete the sentence.	Not agreed. The EMA/CVMP acknowledges that primary research is the pillar of science and that preferentially primary research articles should be cited. As kindly suggested, several statements will be strengthened or balanced with primary research articles when needed. However, the EMA/CVMP considers that high-level reviews published in peer-reviewed journal are also of importance to consider. Numerous primary research papers are also included in the core part of the document.
596–597	6	Comment: This is all extrapolation from in vitro work. This has not been demonstrated other than on a lab bench. Proposed change: Delete the statement or modify the sentence for accuracy.	Agreed. The EMA/CVMP agrees that the main results are only obtained from *in vitro* studies. A more precise text has been added for more clarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
600–602	4	Comment: I was shown by Peeters et al. (2018) that doxycycline (DOX) concentrations of 1 and 4 mg/L can select for resistant *E. coli* in vitro. L. E. J. Peeters, S. Croubels, G. Rasschaert, H. Imberechts, E. Daeseleire, J. Dewulf, M. Heyndrickx, P. Butaye, F. Haesebrouck and A. Smet. 2018. Effect of residual doxycycline concentrations on resistance selection and transfer in porcine commensal Escherichia coli. International journal of antimicrobial agents 51: 123-127.	Not agreed. The EMA/CVMP acknowledges the results of the study as informative. But this paragraph concern mainly evidence of selective concentrations in the environment itself (e.g. soil). The suggested study refer to *in vitro i*nvestigations in laboratory conditions.
600–602	6	Comment: It is good that authors point out that these are in vitro studies – in situ the number of factors affecting this outcome are very large.	Agreed. The EMA/CVMP agrees that the main results are only obtained from *in vitro* studies. A more precise text has been added for more clarity.
605–607	6	Comment: This is a hypothetical statement. Proposed change: Edit to read "may" increase instead of "will" increase.	The EMA/CVMP agrees with the proposal. The wording has been revised accordingly.
611–615	6	Comment: Cleary et al is an artifical study – antibiotics were added directly to soil and no AMR genes were assessed on IntI1 – which is not an ARG	Not agreed. The EMA/CVMP decided to consider any relevant scientific publication. In the study description, it is clearly mentioned that the study is made "on soil experimentally exposed to VMPs".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Rmove sentence and reference due to lack of relevance.	
622–624	4	Comments: Integrons are not mobile by themselves Proposed change: This dissemination of ARGs from antimicrobial-producing organisms to clinically relevant species has occurred within the antibiotic era and is mediated by diverse MGEs (e.g. plasmids, transposons, genomic islands) and integrons~~)~~.	Agreed. The EMA/CVMP notes the comments. The text has been revised accordingly.
623	6	Comment: Stating that this movement of ARGs from antimicrobial producing organisms to clinically relevant species only occurring during the "antibiotic era" is incorrect. AMR bacteria, clinically relevant or not, has been around before the introduction of antibiotics. Proposed change: "has occurred even prior to the introduction of antibiotics…".	Not agreed. This sentence is in response of the sentence just before mentioning that "dissemination of ARGs among commensal and/or pathogenic microbiota during a short period". Thus, the antibiotic era is considered to be a short period.
678–681	6	Comment: It is an assumption these were faecal Enterobacteriaceae. There was never any	Not agreed. It is never mentioned in the document that they present a health risk. But the identification of clinically relevant

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		demonstration these ESBL Enterobacteriaceae were a health risk.	resistant determinants may pose a health risk. Data, specific studies and a risk assessment would be needed to validate this information which is the aim of the document.
757–758	2	Comment: This figure is likely a gross underestimation because it is based on data for only five drug-resistant bacteria. This information should be made transparent when quoting this statistic.	Agreed. The EMA/CVMP notes the comments. The text has been revised slightly for clarity. The sentence now reads: "This issue also imposes an additional healthcare cost and productivity loss that, in the EU, was estimated to be at least €1.5 billion in 2007 which related to the most frequently isolated bacteria from blood cultures in Europe (ECDC/EMEA, 2009)".
785–788	6	Comment: Again, the biological component is also important. Without information about the risk or even just the rate of AMR bacteria that result from exposure to AR then these AR data are of limited value. These data, in addition to the quantitative information about the antimicrobial compounds, are necessary to be able to "valuate the likely stability and persistence of an antimicrobial in the environment and its subsequent potential selection pressure for AMR." Proposed change: This statement is inaccurate and incorrect and should be removed unless information is added about the importance of the biological component – ie if a bacterium in x condition is exposed to x concentration	Agreed. Thank you for your comment. The text has been amended accordingly, now indicating the potential use of fata data in the assessment of AMR development.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of a given AR for X amount of time the rate of development of AMR is X. These issues are nicely laid out in the following paragraph, perhaps authors could add a caveat to the statement above – ie however, it is important to understand biotic factors that influence the rate and development of AMR as discussed in the next paragraph.	
814–816	4	Comments: This sentence should be deleted because it is a duplicate of the sentence above.	Agreed. Thank you for your observation. The duplicate sentence has been removed.
824–825	2	Comment: This is a shortcoming of the pre-approval process that should be addressed. The reflection paper could highlight it as a recommendation rather than observing its absence.	Not agreed. Thank you for your comment. Please note that this issue is addressed in the "assessment section" of the conclusions chapter.
847	6	Comment: 'Safe levels' for antimicrobials (that will not adversely impact human or animal health, or the environment) have not been established for AMR. Proposed change: "Optimized levels" for antimicrobials (that will MINIMIZE adverse impacts on human, animal, or environmental health) have not been established for AMR.	Not agreed. Thank you for your comment, it seems to suggest that apart from "safe levels" there could/should be a weighing of pros and cons, ultimately leading to "optimized levels" that minimize impact. That is possible but would still be hampered by the bullet point as is.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
847–854	2	Comment: HCWH Europe believes that the reflection paper should suggest solution pathways: How could 'safe levels' for antimicrobials be established for AMR? How could comprehensive AMR assessments be performed? How could the lack of appropriate validated essays be overcome? How could the impact on animal/human health and ecosystems be measured?	Not agreed. Thank you for your comment. Please note that this is addressed in the next section.
884–886	6	The statement regarding livestock production being associated with elevated environmental reservoirs of AMR references a review article and should reference a research paper supported by primary empirical data instead.	Not agreed. Thank you for your comment. A review paper is cited here as it combines the results of multiple papers.
895	3	Comment: To really identify knowledge gaps we should research impacts on humans, animals and the environment considering at the same time all kind of uses, *i.e.* human consumption, animal consumption and application on plants/environment. That will allow us to get a clearer picture of the situation, identify interactions and critical control points and propose more proper mitigation measures. While the final and primary goal remains human health, we should acknowledge that in order to be successful we have to approach AMR issue holistically. Unilateral measures can give some positive results,	Thank you for your remark.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		but at the end of the day they will not solve the complex problem of AMR.	
921–938	1	Comment: An alternative method to that proposed by Bengtsson-Palme and Larsson (2016) has been published in Rico et al. (2017), which can be used to derive resistance thresholds and perform preliminary risk assessments in environmental compartments. I suggest revising the paper and adding the text provided below (or similar) at the end of the paragraph. Reference: Rico, A., Jacobs, R., Van den Brink, P. J., & Tello, A. (2017). A probabilistic approach to assess antibiotic resistance development risks in environmental compartments and its application to an intensive aquaculture production scenario. Environmental Pollution, 231, 918-928. 10.1016/j.envpol.2017.08.079 Proposed change: Rico et al. (2017) proposed an alternative method to derive resistance thresholds based on theoretical MSC distributions, which are derived from MIC data in a similar way as proposed by Bengtsson-Palme and Larsson (2016). The method provided by Rico et al. (2017) is grounded on probabilistic risk assessment theory and can be used to calculate the probability that antibiotic exposure concentrations result in antibiotic resistance at the community level. The	Agreed. Thank you for the additional information, the suggested addition has been added to the end of the section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		method can be used to perform preliminary risk assessments in environmental compartments with measured or modelled exposure concentration distributions.	
925–928	6	Comment: There are not just "some concerns, regarding the ability to extrapolate results from in vitro competition experiments to the 926 complexity of microbial communities in the environment." This is a fundamental hurdle to being able to provide any "predictive" or even "surveillance" capacity with regards to occurrence and development of environmental AMR. Proposed change: Suggest that any reference to use of in vitro data to speculate on environmental situations be removed.	Not agreed. Thank you for your comment. The principle – and drawbacks – of applying in *vitro test* results to assess environmental risks is not unique to AMR but underlies all chemical risk assessments. Therefore, we touch on the existing approaches, and associated concerns are indicated and (theoretical) alternatives are brought forward in the rest of the section.
948–995	3	Comment: Proper disposal of unused VMPs and containers should be causes of environmental contamination and therefore mitigation measures, such as raising awareness about their responsible disposal should be considered. Proposed change: Add recommendation for best practices in disposal of VMPs.	Agreed. Thank you for your comment. Proper disposal has been added as one of the RMMs.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
961–972	2	Comment: HCWH Europe welcomes the 2006 EU-wide ban on antibiotic use as growth promoters in animal feed. This was an efficient and useful measure to curb the unnecessary use of antibiotics in animal farming. As indicated above, HCWH Europe suggests to include the promotion of sustainable farming conditions across the EU as a mitigation measure.	Agreed. Thank you for your comment. Enhancing animal welfare related to reduction of microbial infections has been added as one of the options to reduce the quantities of antimicrobials used.
973–987	2	Comment: Scientific studies consider that the spreading of manure is one of the most significant factors for the emergence of horizontally transferrable resistance determinants within veterinary practices. HCWH Europe therefore calls for the reflection paper to highlight the need to determine good application and storage practices in its conclusions.	Partially agreed. Thank you for your comment. Please note that this issue is addressed in the conclusions chapter under "Assessment of the risk".
982–983 & 992	4	Comments: Besides anaerobic digestion of liquid manure to produce biogas, in some regions with a dense pig population and therefore a high surplus of N (ammonia), a large fraction of the pig manure is treated in biological manure treatment systems. In Europe, 6.4% of the total manure production was treated through anaerobic digestion (biogas) in 2010, making this the most used technique. Treatment of the liquid fraction, as occurs during	Agreed. Thank you for this additional information. Manure treatment systems are now more specifically addressed in the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		biological removal of nitrogen from manure, accounted for 0.7% of the total livestock production in Europe (Foged et al., 2011). As Flanders is listed as a Nitrate Vulnerable Zone (NVZ), this region in Belgium struggles with a significant N surplus and therefore biological removal of nitrogen is a typically used system as anaerobic digestion still leaves an effluent with high N content(Bortone, 2009; European Commission, 2018). In Flanders, a total of 44.1 kt N was treated in 124 plants and biological removal of nitrogen was the most used technique to process swine manure in 2016. Biological N removal from swine manure is a process of about 35 days. The raw manure first goes into the centrifuge where it is separated in a solid and a liquid fraction. The solid fraction is mostly composted and/or exported and the liquid fraction undergoes the biological nitrogen removal. This is a process of nitrification and denitrification which can be separated in space or in time. During nitrification, ammonium (NH4+) is converted to nitrate (NO3-) by nitrifying bacteria in the presence of oxygen. During denitrification, denitrifying bacteria use the oxygen attached to the nitrate molecule for respiration, creating nitrogen gas as a byproduct. The effluent is used as a potassium fertilizer for certain crops. The use of effluent may also promote the dissemination of antibiotic resistance genes as these	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		are still present in this type of matrix, although the levels are lower than in the raw manure. This implies that the practice of biological manure treatment in order to alleviate the N surplus may inadvertently increase the dissemination of antibiotic residues, antibiotic resistance genes and zoonotic bacteria into the environment if the effluent is used in combination with raw manure. Likewise as for anaerobic digestion, also for biological N removal from swine manure, the process should be optimized with a focus on elimination or decrease of residues and/or AMR. A relevant reference (as already mentioned above) is: T. Van den Meersche, G. Rasschaert, F. Haesebrouck, E. Van Coillie, L. Herman, S. Van Weyenberg, E. Daeseleire and M. Heyndrickx. 2019. Presence and fate of antibiotic residues, antibiotic resistance genes and zoonotic bacteria during biological swine manure treatment. Ecotoxicology and Environmental Safety, 175: 29-38.	
996–1010	3	Comment: We very much agree with the conclusion. Before acting, it is important to understand where most of the burden on the environment is coming from and to better understand the pathways and epidemiology.	Agreed. Thank you for your comment. Please note that "One Health" is addressed in the next section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		We suggest to do all research in a real 'one health' way, looking at the impact of all antibiotic production, consumption and disposal. Proposed change: Add reference to do further research and recommendations following this in a real 'one health way'.	
1000	6	Comments: This contradicts earlier statements on "data gaps". See lines 856-860 that clearly articulate the current situation. This white paper on one hand acknowledges that there is very little to no empirical data regarding the impact of Ag antimicrobial use on "Environmental AMR" but on the other hand (in these conclusions) uses the worst case scenario extrapolation in many non-primary research publications to suggest that environmental AMR is a prominent risk driven by agricultural antimicrobial uses. Proposed change: Repeat lines 856-860 here for consistency instead of coming to a different conclusion than what the paper acknowledges earlier.	Agreed. Thank you for your comment, the suggested lines have been added to the conclusions section.
1013–1017	3	Comment: It is not correct to compare volumes, as the JIACRA report does, need to be done via biomass. 'JIACRA: In	Not agreed. Thank you for your comment. Please note that while the doses would be comparable but the volumes are larger, the

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		2014, the average AMC was higher in animals (152 mg/kg) than in humans (124 mg/kg), but the opposite applied to the median AMC (67 and 118 mg/kg, respectively). In 18 of 28 countries, AMC was lower in animals than in humans.' Proposed change: Use biomass.	contribution to AMR is still larger as the antimicrobials are applied in more cases.
1013–1017	6	Comment: Throughout this paper and even in the proceeding paragraph authors point out the complexity of understanding the effect of AR on AMR and in trying to pinpoint input sources and their relative importance. In this paper, authors did not show supportable data to substantiate the statement the VMA "contributes to environmental reservoirs of ARB that can directly or indirectly drive the transference of MGEs to humans and animals." Proposed change: Accurately describe the uncertainty that remains.	Not agreed. Thank you for your comment. Please note that the references of Cantas et al. (2013) and Wellington et al. (2013) have been brought forward to support the statement that ARGs in the environment complex and diversified reservoir of resistance genes that can be transferred into and between environmental and clinically relevant bacteria. Furthermore, in the introduction is stated that this paper considers the impact of ARGs in the environment resulting from the use of VMPs. ARB is changed to ARG.
1036–1037	6	Comment: Any reference to or use of in vitro data to speculate about what would occur in an environmental setting is something that must be critically evaluated and should be based on controlled studies that validate any data – even on a per compound basis. Given the	Not agreed. Thank you for your comment. As also replied to your comment to line 925-928, the principle – and drawbacks – of applying *in vitro* test results to assess environmental risks is not unique to AMR but underlies all chemical risk assessments. Therefore, we touch on the existing

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		acknowledged complexity of environmental exposures/risks/dissemination – it is difficult to understand how boiling this entire sector down to this level of simplicity can be scientifically valid.	approaches, and associated concerns are indicated and (theoretical) alternatives are brought forward in the rest of the section.
1038	6	Comments: Again, research that describes how treated and untreated animals shed similar AMR levels should be cited and acknowledged for an unbiased description of the issue. Proposed change: Add statement to emphasize that treated and untreated animals shed similar AMR levels. Suggested citation Vikram et al Appl Environ Microbiol (2017) 83:e01682-17 – others can be provided if needed.	Agreed. Thank you for your comment. The statement in the second bullet has been adapted.
1096	6	Comment: The Berkner paper is another review article. Proposed change: Suggest quoting studies that provide empirical evidence rather than a review article if looking to establish scientific credibility for this work.	Not agreed. Thank you for your comment. Please note that review papers have been cited as they combine the results of multiple papers. This is considered a more efficient way to cover many years of research.
1105–1127	6	Comment: Some of the statements in this section about metals are broadly stated yet the data on which they are based seem more specific and limited. Also, only one	Not agreed. Thank you for your comment. Please note that this section only provides a short overview of issues related to metals. It is not the intention to provide a full review and it is

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		article by one author is referenced, and primary articles are not referenced. In addition, the section gives the impression that zinc and copper are net bad, yet does not consider benefits. The US Food and Drug Administration and Environmental Protection Agency have approved certain uses, e.g., food additives (https://www.fda.gov/food/food-additives-petitions/food-additive-status-list), medical devices (example: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018680), surfaces in healthcare facilities https://www.epa.gov/pesticide-registration/updated-draft-protocol-evaluation-bactericidal-activity-hard-non-porous). Some of the statements in this section are so general that they give the impression of implications for all of these uses. Where there is not data available or reviewed, the section should make clear that it is not addressing these other uses.	considered that no such impression is given in the current section.
1132 (Glossary)	7	Comment: The VICH explanation contains some figures within the sentence that do not make sense. Proposed change: VICH is a trilateral (EU-Japan-USA) programme aimed at harmonising technical ~~2949~~ requirements for veterinary product registration. Its full title is the International ~~2950~~ Cooperation on Harmonisation of	Agreed. Thank you for your observation. Amendments have been made accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Technical Requirements for Registration of ~~2951~~ Veterinary Medicinal Products.	
1312–1315 (References)	7	Comment: The latest report was published in October 2018; see also comment on line 255. Proposed change: ~~EMA/ESVAC. 2017. European Medicines Agency, European Surveillance of Veterinary Antimicrobial 1312 Consumption. Sales of veterinary antimicrobial agents in 30 European countries in 2015 1313 (EMA/184855/2017). Trends from 2010 to 2015. Seventh ESVAC report. In 1314 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/10/WC500236750.pdf.~~ EMA/ESVAC. 2018. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. Sales of veterinary antimicrobial agents in 30 European countries in 2016 (EMA/184855/2017). Trends from 2010 to 2016. Eighth ESVAC report. In https://www.ema.europa.eu/documents/report/sales-veterinary-antimicrobial-agents-30-european-countries-2016-trends-2010-2016-eighth-esvac_en.pdf.	Agreed. Thank you for your comment. The reference has been updated to the latest report.
Figure A1	6	Comment:	Not agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This figure is speculative and of little value in understanding the complexity of interactions between bacteria, antibiotic and environment. In contrast, the UK Department of Health "AMR Systems map" is highly relevant. Proposed change: Recommend removing.	Thank you for your comment. As the figure is discussed in the section below the figure, it is considered relevant for the section.
Figure 1	6	Comment: Antibiotics are definitely used prophylactically in humans. See: Antimicrobial Prophylaxis in Adults" Mayo ClinProc. 2011 Jul;86(7):686-701 Proposed change: Should add preventative use to human side. The definition of therapeutic includes prevention in some countries as prevention of disease is considered therapeutic.	Agreed. Thank you for your comment. The term "therapeutic" has been removed from the figure.
Figure 2.	6	Comment: Why is there a Human Consumption component to this figure if it is meant to show "emissions and fate of antimicrobials in the environment following use of VMP"?; Aquaculture use is still " veterinary consumption"; the surface water/sediment and soil connections are odd since animal uses release to water and human uses release to soils. In general this	Agreed Thank you for your comment. The figure is deleted from the paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		is a confusing figure that doesn't directly address the point? Proposed change: Perhaps delete the figure?	
Table 3	6	Comment: This table should be removed. The questions are fine and well laid out throughout the paper the "some Suggestions" column has no basis given the stated need for research (the gaps that need to be filled). Re-listing gaps is of little use. Many of the "some suggestions" are speculative and argumentative – ie animals as sources of contaminants versus sewage? Concentrations of antibiotics that induce HGT – purely speculative as the dose-outcome have not been established and certainly not for environmental situations. Dissemination routes – what is the basis for statement "Water bodies and agriculture have large potential"? In addition: 1) the third row stating that animals given antibiotics is the likely environment to study overlooks research that shows similar AMR levels in animals that are and are not given antibiotics (https://www.ncbi.nlm.nih.gov/pubmed/30476443 ;	Not agreed. Thank you for your comment. The table contains suggestions and is considered a useful overview helpful for discussions on this topic. 1) Please note that the table considers AMR by VMP use. The issue you raised is already addressed in another section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		https://www.ncbi.nlm.nih.gov/pubmed/30109957 ; https://www.ncbi.nlm.nih.gov/pubmed/28887421). 2) the fourth row mentions transfer and movement of resistance: We have long known that mobile genetic elements (MGEs) play some role in AMR spread but there is no evidence to link the existence of MGEs to animal antimicrobial uses. Proposed change: Suggest removing table. At the least – the following statement should be removed as it is conjecture based on no data – knowledge gaps that need to be filled with regards to that statement are well laid out in the paper – Remove statement: "The spreading of manure is considered as most significant for VMPs." Also, "Which environments have potential to drive resistance selection.." – the Likely versus Possible are really just speculation without the data – how it is that sewage, waste disposal are a "possible" source while "animals given antibiotics are a "likely" source has no basis.	2) The table gives suggestions. This is one of the issues to investigate.
Table 3	6	Comment: Citations ignore Ignores research that AMR levels are very similar in animals that are not given antibiotics and paucity of evidence to link the existence of MGEs to animal antimicrobial uses. Proposed change:	Not agreed. Thank you for your comment. The table contains suggestions and is considered a useful overview helpful for discussions on this topic.

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		Suggest removing table 3.	