Critical review of AMR risks arising as a consequence of using biocides and certain heavy metals in food animal production: Mitigation strategies, Conclusions and Reccomendations

Mitigation strategies

As Singer et al. (2016) stated “[the] understanding of AMR in the environment is so unsatisfactory that there is very little that can be suggested for mitigation without employing the precautionary principle as the primary rationale for action”. This remains the case and we would echo that statement. A better understanding of how biocides and/or heavy metals can influence AMR and ARGs in the primary food production environment is needed to inform the development of effective mitigation measures. As highlighted by Maillard (2020), and others, there is a conundrum that while the use of biocides is important to control microbial pathogens inappropriate applications may lead to an exacerbation of AMR. Similarly, the use of heavy metals in food animal production provide benefits (particularly to animal health), but may contribute to the spread of AMR.

Overall, when considering the use of biocides and heavy metals in food animal production and mitigation strategies, a clear distinction should be made between the risk of acquired antibiotic cross-resistance and co-selection through the use of sub-inhibitory supplementary concentrations of heavy metals and biocide and their use at concentrations that kill or inactivate. While biocides are in the main applied at killing or inactivation concentrations, some may be used in feed. In the main heavy metals are used at sub-inhibitory supplementary concentrations and will be present in the environment at these concentrations, and it is possible that some may be used at killing or inactivation concentrations in medical treatments.

Use of biocides in food animal production

Despite current gaps in knowledge, action can be taken to mitigate potential risks by providing clear guidance to manufacturers and users of biocidal products on practices aimed at minimising the potential development of resistance. For example, the appropriate use of biocides in keeping with the manufacturer’s instructions and the intended product use, and validation of effectiveness specific to the application. Improper or excessive use of biocides, and use at sub-inhibitory concentrations in the food production chain should be avoided as it may drive the emergence of AMR. It would be prudent for manufacturers of biocides used in food animal production to investigate whether cross-resistance to clinically-important antimicrobials is likely to occur under conditions of prescribed use.

Use of heavy metals in food animal production

While there are gaps in knowledge, effective strategies should focus on a reduction in the heavy metal input/output ratio in livestock and aquatic farmed animals. Recent reductions in permitted

concentrations and a ban on therapeutic use are mitigation strategies that are already in place and should reduce risk. There is still a need to establish whether current concentrations in food animal production in the UK represent any real hazard with respect to the selection of AMR. Formulated diets that increase the efficiency of nutrient retention by animals, decrease their excretion in faeces and urine and reduce the import of nutrients in feed and mineral mixtures are still important mitigating strategies. Different approaches to reduce the content/impact of heavy metals in manure/slurry have been studied but optimum mitigation strategies not yet confirmed. Additional research is needed to determine optimum methods in a UK context for reducing/eliminating heavy metals and antimicrobial-resistant bacteria, ARGs, and HMRGs from stored manure/slurry prior to use in the environment. A recent EFSA report also highlighted that such measures may increase storage and equipment resources requirements and may reduce the fertiliser value of the manure/slurry (EFSA BIOHAZ Panel, 2021).

Conclusions

On reviewing the published evidence, our conclusions regarding the project's four key questions (terms of reference) are thus:

Is there evidence to show that biocides and heavy metals used in food animal production have an impact on the development of AMR?

We have found that there is some evidence that biocides and heavy metals used in food animal production may have an impact on the development of AMR and either resulting in reduced susceptibility to drugs or clinically significant resistance. There is more compelling evidence regarding the use of heavy metals than there is on the use of biocides.

How long are biocides and heavy metals able to persist in animal production environments and how does this impact on the development of AMR and associated risks?

There is evidence that heavy metals will persist, accumulate, and may impact on the development of AMR in animal production environments for many years. There is less evidence on the persistence and impact of biocides. There is some evidence that while many biocides will rapidly break-down in the environment, some, such as QACs, may persist. There is little evidence on how long this persistence may be in animal production environments, and what the impact on AMR may be.

What evidence is there that biocide and heavy metal associated AMR enters the food chain through products of animal origin or as a result of crop contamination?

There is no clear evidence of biocide and/or heavy metal associated AMR entering the food chain, through products of animal origin or as a result of crop contamination due to their use in food animal production. Published studies that have demonstrated an association between biocide and/or heavy metal use and increased AMR/ reduced susceptibility risk in live animals, manure, slurry, or soil have not looked beyond these points at how this use may impact on AMR risk in food. Although there is evidence of the co-carriage of BRGs/HMRGs and ARGs in retail meats.

Is there a potential risk to the consumer from AMR acquired through the use of biocides and heavy metals in food animal production?

It is recognised that AMR in food is a risk to consumer health, and that food animal production has an impact on this risk. While there is certainly a theoretical risk, we have found no published evidence that has specifically demonstrated that the use of biocides and/or heavy metals in food animal production increases the risk of the consumer acquiring antimicrobial-resistant bacteria from food or has quantified that risk. There does not appear to be sufficient evidence to

undertake such an assessment of risk.
A central question was whether the release of chemicals like biocides (in particular disinfectants) and/or heavy metals from food animal production has the potential to create local concentrations where AMR can emerge and spread (as bacteria or genes) and whether this presents a potential risk to the consumer as a result. In our opinion there does appear to be sufficient evidence that that this is possible and that there is a potential risk to the consumer. Nevertheless, there do not appear to be sufficient data to undertake such an assessment of risk and focussed in-field studies need to be carried out to fill this evidence gap and provide the data required to assess this risk.

Recommendations

The NAP highlighted that this subject (the role of heavy metals and other biocides in the environment in promoting AMR) remains an evolving area of research that requires further study. This remains the case.
While recognising that similar recommendations have been in past reviews of this subject (Table 4). In our opinion the following studies are required to improve our understanding of the role of biocides and heavy metals used in food animal production have in promoting AMR:

- To determine the amounts, types, and concentrations of biocides used in terrestrial food animal production and aquaculture in the UK and whether biocides persist in these environments, and at what concentrations.
- Implementing the monitoring of copper and zinc pollution from agriculture in areas in which food-producing animals are fed (including aquaculture), with particular attention to the potential development of microbial AMR in the environment. The data would help to identify any area under risk.
- Monitoring the occurrence of biocide/heavy metal tolerance and cross- and co-resistance in bacteria isolated from terrestrial food animal production and aquaculture environments in the UK.
- To determine the thresholds for biocide and heavy metal concentrations (MSCs) that could co-select for AMR in the animal production environment (including the aquatic environment), animal waste, manure, and manure enriched soils.
- To determine optimum methods in a UK context for reducing/eliminating heavy metals and antimicrobial-resistant bacteria, ARGs, and HMRGs from stored manure/slurry prior to use in the environment.
- To access through controlled longitudinal in-field trials whether there is a causal impact on the use of biocides and/or heavy metals used, at different concentrations, in food animal production (land and aquatic), impact on AMR selection and transmission in food animals and transfer to foods of animal origin, and impact on AMR selection and transmission in agricultural soil and subsequent transfer to crops and foods of plant origin to determine the risk.
- Applying culture independent approaches, such as shotgun metagenomics and exploring metagenomes, to examine samples and explore correlation more widely in less well characterised bacterial communities for BRGs/HMRGs and ARGs.