Critical review of AMR risks arising as a consequence of using biocides and certain heavy metals in food animal production: Knowledge gaps and uncertainties

Several uncertainties have been identified related to the probability of co-selection of, and transmission of, AMR due to the use of biocides and heavy metals in food animal production. Many of these are caused by knowledge and data gaps, and the limitations of the published studies identified and reviewed. Such gaps have also been identified in numerous other reviews, including those listed in Table 4, and SCENIHR (2010) amongst others. Conclusive evidence of the impact of the use of biocides and heavy metals in food animal production on AMR cannot be established because of the high level of uncertainty in the literature. As highlighted in other similar reviews (such as SCENIHR, 2010; Davies & Wales, 2019; FAO/WHO, 2019; EFSA BIOHAZ Panel, 2021) it is clear that more robust experimental strategies and testing are needed to identify risk. Intensive agricultural activities are likely to contribute to the selection and development of AMR but further evidence, particularly in the UK context, is needed.

Overall, there is a particular lack of evidence on how biocides and heavy metals may impact on AMR in aquaculture that needs to be addressed. It is likely that much of the work done in the context of general terrestrial systems will not apply to aquaculture where environmental conditions are different and both bacteria and agents likely to behave differently. The impact of different aquaculture systems, for example marine or land based Recirculating Aquaculture Systems (RAS), need to be addressed.

There is compelling theoretical and laboratory experimental evidence that certain biocides may co-select for AMR. Studies that have investigated the effects of biocides on the development of AMR are predominantly laboratory-based, and translation to real-world environmental conditions is both difficult and limited. Longitudinal studies on the impact of biocides during animal production on the co-selection and transmission of AMR to animals and foods of plant and animal origin are lacking.

It is frequently cited in the literature that some biocides may leave residues that could co-select for AMR (FAO/WHO, 2019). Therefore, such biocides may be less appropriate for use in food animal production due to their potential for impact on the environment and the potential emergence of resistance. It is unclear in the literature what specific biocides may present such a risk and there are no data on whether biocides used in food animal production persist in the food animal production environment. It is unclear how long biocides can persist in the environment, at what concentration, and especially what (minimum or threshold) concentration can trigger AMR selection, and how this may be affected by environmental conditions.

Within the UK context there are insufficient data about the amounts and types of biocides used in terrestrial food animal production and aquaculture. This is important for informing future studies in the field or laboratory to provide robust data to assess the risk of such products on AMR

selection.
There is compelling evidence that heavy metals will persist, accumulate, and may impact on the development of AMR in animal production environments for many years. Longitudinal studies on the impact of heavy metals during animal production on the co-selection and transmission of AMR to animals and foods of plant and animal origin are lacking. Permitted concentrations of zinc and copper used in food animal production have been reduced in recent years in the UK. It is unclear as to whether this has reduced the risk of these metals driving the selection and transmission of AMR.

There is evidence that levels of biocides and heavy metals need to accumulate to critical concentrations (MSCs) before they can trigger co-selection of AMR. As highlighted by the FAO and WHO (FAO/WHO, 2019) and Arya et al. (2021), there are little data on what these threshold values should be in order to inform suitable standards for biocide/heavy metal concentrations in food animal production.

It has been theorised that heavy metals in certain forms (as stable metal compounds that do not release free metal ions) may provide nutrition to food-producing animals but not be toxic to bacteria, and hence their use in feed would not co-select for AMR in bacteria (Yu et al., 2017). There does not appear to be any published evidence supporting this hypothesis.

A further issue is that many studies when examining isolates apply different methodologies and criteria for determining resistance/tolerance to biocides and heavy metals. There is a clear need for standardisation of methodology for both examining isolates and for also determining the concentration of agents within samples and concordance of resistance/tolerance phenotype with BRGs and HMRGs. A greater understanding of the nature and behaviour of biofilms in the field on the persistence and transmission of AMR is also required. The effects of field biocides on MGEs (such as plasmids) carrying resistance genes and the potential for HGT from MGEs that may persist following cleaning and disinfection also need to be explored.

Furthermore, many studies focus on a narrow range of bacteria and ignore the wider microbial community and upon which heavy metal and biocides could be exerting co-selection of AMR within the community or facilitating transfer of AMR via HGT.