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

Antimicrobial resistance (AMR) is the resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it, so that standard treatments become ineffective, and infections persist, increasing the risk of spread to others and negative clinical outcomes. AMR is a complex issue driven by a variety of interconnected factors enabling microorganisms to withstand the killing or microstatic effects of antimicrobial treatments, such as antibiotics, antifungals, biocides, and preservatives. Microorganisms may be inherently resistant to such treatments or can change and adapt to overcome the effects of such treatments. Microorganisms can acquire AMR due to mutation or through horizontal gene transfer (HGT) via several mechanisms. The widespread use of antimicrobials in clinical practice and especially in intensive food animal production is known to result in selection and dissemination of AMR in microorganisms. AMR and antimicrobial resistance genes (ARGs) are a major public health issue worldwide and it is estimated that unless action is taken to tackle AMR, the global impact of AMR could be 10 million deaths annually by 2050 and an associated cost of up to US $100 trillion in terms of cumulative lost global production (O'Neill, 2016).

Biocides are active chemical molecules (agents) that control the growth of, or kill, bacteria and other microorganisms. Disinfectants and sanitisers are forms of biocides. Biocides are used for a number of reasons in animal production including, the cleaning and disinfecting of buildings and equipment as well as decontaminating ponds and equipment in fish farming. The primary use of heavy metals, such as copper and zinc, in food animal production are as nutritional additives in animal feed but they may be used in livestock footbaths and to treat skin problems such as dermatitis. Some biocides and heavy metals used in animal husbandry can persist and concentrate in the environment, remaining stable for prolonged periods. It is a concern that bacteria can exhibit tolerance to these chemical and metal elements and that the genes encoding for these phenotypes can be located on mobile elements that may contain one or more AMR-encoding genes, thereby co-selecting for AMR (as highlighted in the NAP).

This study was undertaken to critically review the available scientific literature for assessing whether, and to what extent, the single or combined effects of using widely available biocides for sanitation and heavy metals in animal feed and other uses (such as therapeutically and to treat infections) during food animal production leads to the development and spread of AMR within the food chain. Whether this usage could potentially lead to greater consumer exposure to antimicrobial-resistant bacteria from food, either directly through consumption of foods derived from animals that have undergone treatment (for example from the use of heavy metals in animal feed) or indirectly (for example from exposure of crops to contaminated soil or ground water) is also discussed.

The review question was defined as:

“Do biocides and/or heavy metals used in food animal production have an impact on the development of AMR in the food chain?”

A systematic review approach was taken to the literature search. The review adopted a comprehensive search strategy considering all available evidence in the public domain, including peer-reviewed articles, grey literature (for example, government and industry reports), relevant government reports (for example, FSA published studies, ACMSF reports), European and International literature (for example, the EFSA Scientific Opinions, WHO reports) up to February 2023. Three scientific literature databases (Web of Science, Scopus, and MEDLINE) were searched for relevant publications, supplemented by focused Google and Google Scholar s earches, searching within relevant publications, and through contact with authors. A total of 3,434 of publications were identified, which were reduced to 550 after screening the titles and abstracts. This total was further reduced to 148, from which some data were extracted after appraising the full publications. Due to the range of publications identified, the paucity of specific published studies, and different laboratory methodologies used in these studies, a narrative approach was taken to their review and to the review of supplementary materials.

The review was structured and aimed at addressing the following key questions (terms of reference):

1. Is there evidence in the literature to show that biocides and/or heavy metals used in food animal production have an impact on the development of AMR?
2. How long are biocides and/or heavy metals (used in food animal production) able to persist in animal production environments, and how does this impact on the development of AMR and associated risks?
3. What evidence from the literature is there that biocide and/or heavy metal-associated AMR enters the food chain through products of animal origin or as a result of crop contamination?
4. Is there a potential risk to the consumer from AMR acquired through the use of biocides and/or heavy metals in food animal production?

On reviewing the published evidence our conclusions regarding these four key questions are that:

1. We have found that there is some evidence that both 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.
2. We have found that 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. 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 quaternary ammonium compounds (QACs), may persist. However, there are little data on how long and at what concentration such agents may persist in animal production environments, and what the impact on AMR may be.
3. We have not found any 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 biocide and heavy metal resistance genes and ARGs in retail meats.
4. We have found that there is evidence that AMR in food is a risk, and that food animal production has an impact on AMR risk. However, 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 AMR or has indeed quantified that risk. Currently there does not appear to be sufficient evidence to carry out 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 this is possible and that there is a potential risk to the consumer. However, currently there does not appear to be sufficient data to carry out an assessment of risk, and there is a clear need for focussed in-field studies (as detailed in this report) to be carried out to fill this evidence gap and provide the data required to assess this risk.