Annex to:
EFSA BIOHAZ Panel (EFSA Panel on Biological Hazards), Koutsoumanis K, Allende A, Alvarez-Ordóñez A, Bolton D, Bover-Cid S, Chemaly M, Davies R, De Cesare A, Herman L, Hilbert F, Lindqvist R, Nauta M, Ru G, Simmons M, Skandamis P, Suffredini E, Andersson DI, Bampidis V, Bengtsson-Palme J, Bouchard D, Ferran A, Koubia M, López-Puente S, López-Alonso M, Nielsen SS, Pechová A, Petkova M, Girault S, Broglia A, Guerra B, Innocenti ML, Liébana E, López-Gálvez G, Manini P, Stella P and Peixe L, 2021. Scientific opinion on the maximum levels of cross-contamination for 24 antimicrobial active substances in non-target feed. Part 1: Methodology, general data gaps and uncertainties. EFSA Journal 2021;19(10):6852, https://doi.org/10.2903/j.efsa.2021.6852
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Annex E. Extensive literature search on the potential growth promoting effects of 24 antimicrobial active substances

1. Objective of the review
1.1. Literature search

The extensive literature review conducted within the framework of this project was implemented according to the principles of a systematic review. The need for practical applications to be evidence-based has been strongly increasing since the 1990s which in turn led to an increasing number of published (systematic) reviews. The methodology and guidelines were developed in the medicinal discipline and subsequently adopted for other fields (Arksey et al., 2005; Sargeant et al., 2005; CRD, 2009; FDA, 2009; EFSA, 2010; Levac et al., 2010; Bragge et al., 2011; Cochrane, 2011; Hidalgo Landa et al., 2011; CECB, 2013; Daudt et al., 2013; Kohl et al., 2013; BAuA, 2014; Miake-lye et al., 2016; Hoffmann et al., 2017). The systematic approach is not limited to scientific publications but can also be applied to grey literature (Godin et al., 2015).

Depending on the desired type of systematic review (narrative review, scoping review, meta-analysis etc.), the process may take (alterations of) up to eight steps:
1. Preparation and creation of review protocol
2. Identification of studies in literature search
3. Selection of studies according to inclusion and exclusion criteria
4. Extraction of the studies’ data/results
5. Evaluation of the studies’ quality
6. Charting the results and other descriptive summary measures
7. Data synthesis/synopsis and analysis (qualitative or quantitative; e.g. meta-analysis, best evidence synthesis)
8. Presentation, interpretation and reporting of the results

Within the framework of this project, an ‘extensive literature search’ was conducted, requiring a focus on steps 1-3.

1.2. Review question – concepts and key elements

The review question is of the PICO (Population – Intervention – Comparator – Outcome) type (EFSA, 2010; Aiassa et al., 2015) (Table 1).
### Table 1: Definition of the key elements

| Concepts/Key elements | Inclusion                                                                 | Exclusion                              |
|----------------------|---------------------------------------------------------------------------|----------------------------------------|
| **Population**       | Food producing animals:                                                  | Human                                  |
|                      | - Ruminant: growing and dairy (cattle, sheep, goats, buffaloes),          | Non-food producing animals             |
|                      | - Avian species: chickens and turkeys for fattening; laying hens; minor avian species (ducks, guinea fowl, geese, quails, pheasants, ostrich) |                                        |
|                      | - Pigs: weaned, growing and reproductive                                  |                                        |
|                      | - Fish: salmon; trout; other farmed fish (seabass, seabreams, carp), crustaceans |                                        |
|                      | - Equine                                                                  |                                        |
|                      | - Rabbits                                                                 |                                        |
|                      | - Other species identified as relevant during the literature search       |                                        |
| **Intervention/Substance** | Amoxicillin                                                              | Unspecified mixtures                    |
|                      | Amprolium                                                                 |                                        |
|                      | Apramycin                                                                 |                                        |
|                      | Chlortetracycline                                                         |                                        |
|                      | Colistin                                                                  |                                        |
|                      | Doxycycline                                                               |                                        |
|                      | Florfenicol                                                               |                                        |
|                      | Flumequine                                                                |                                        |
|                      | Lincomycin                                                                |                                        |
|                      | Neomycin                                                                  |                                        |
|                      | Spectinomycin                                                             |                                        |
|                      | Sulfonamides                                                              |                                        |
|                      | Tetracycline                                                              |                                        |
|                      | Oxytetracycline                                                           |                                        |
|                      | Oxolinix Acid                                                            |                                        |
|                      | Paromomycin                                                               |                                        |
|                      | Penicillin V                                                              |                                        |
|                      | Tiamulin                                                                 |                                        |
|                      | ThiampHENicol                                                             |                                        |
|                      | Tilmicosin                                                                |                                        |
|                      | Trimethoprim                                                              |                                        |
|                      | Tylosin                                                                   |                                        |
|                      | Valnemulin                                                                |                                        |
|                      | Tylvalosin                                                                |                                        |
| **Intervention/ Level** | Use levels of the antimicrobials                                          |                                        |
| **Intervention/ Route** | Oral administration: medicated feed, water                               | Other than oral administration         |
| **Comparator**        | Negative/ positive control group, different levels of application        |                                        |
| **Outcome**           | Average daily gain/final weight, feed intake, feed efficiency             |                                        |
|                      | Feed intake, feed efficiency, feed intake /milk, milk yield, fat/protein yield |                                        |
|                      | Feed intake, feed efficiency, feed intake /egg mass, egg production, egg weight |                                        |
|                      | Carcass weight, carcass yield, relative weight of the (different sections of) intestine |                                        |
|                      | Utilisation of some nutrients (DM, Ca, P), digestibility                 |                                        |
|                      | Homogeneity of the flock/herd                                             |                                        |
### Concepts/Key elements

| Inclusion                                      | Exclusion                                           |
|------------------------------------------------|-----------------------------------------------------|
| Health, i.e. reduction of morbidity and/or mortality | Other endpoints identified as relevant during the literature search |

Other inclusion and exclusion criteria and restrictions comprise the year and the language of publication and the publication type (*Error! Reference source not found.*).

#### Table 2: Inclusion/exclusion criteria for further elements

| Concepts/Key elements | Inclusion                                      | Exclusion                                           |
|-----------------------|------------------------------------------------|-----------------------------------------------------|
| **Time**              | No time limits                                 |                                                     |
| **Language**          | English                                        | Other language than English, and no abstract in English |
|                       | Other language, but abstract in English        |                                                     |
| **Publication type**  | Primary research studies (i.e. studies generating new data), PhD Theses, Systematic reviews (only for identification of primary studies), Narrative reviews, Expert opinions/Authority | Books and book chapters, Expert opinions, editorials, and letters to the editor, Extended abstracts, conference proceedings |
|                       |                                               |                                                     |
| **Access**            | full text                                      | no full text available                              |

### 2. Method

#### 2.1. Search strategy

For the search, the 'splitting' approach will be applied, i.e. a series of search strategies designed to capture each individual substance (Intervention) will be performed.

#### 2.3.1. Search terms and search string

The search strategy will allow for searching of the title, abstract, keywords and subject indexing terms (if available). The search terms are selected to incorporate a wide variety of synonymous and related terms. Truncation and wildcards will be used where appropriate to capture different conventions in spelling and variation in the endings of terms. Search strings will be combined with Boolean and proximity operators appropriate for the scope of the review.
| Set | Field | Search String | MeSH terms | Concepts/ Key Elements |
|-----|-------|---------------|------------|-----------------------|
| #1 | Topic | ruminant OR ruminants OR cattle OR beef OR cow OR cows OR calves OR sheep OR lamb OR lambs OR goat OR goats OR buffalo OR buffalos | "Ruminants"[Mesh] | Population/ Ruminant |
| #2 | Topic | bird OR birds OR avian OR chicken OR chickens OR duck OR ducks OR goose OR geese OR turkey OR turkeys OR poultry OR hen OR hens OR broiler OR broilers OR fowl OR ostrich OR ostriches OR pheasant OR pheasants OR quail OR quails OR pigeon OR pigeons | "Birds"[Mesh] | Population/ Avian species |
| #3 | Topic | swine OR pig OR pigs OR piglets | "Swine"[Mesh] | Population/ Pigs |
| #4 | Topic | fish OR fishes OR crustacea OR crabs | "Fishes"[Mesh] OR "Crustacea"[Mesh] | Population/ Fish |
| #5 | Topic | horse OR horses OR equid OR Equidae | "Horses"[Mesh] | Population/ Equine |
| #6 | Topic | rabbit OR rabbits | "Rabbits"[Mesh] | Population/ Rabbits |
| #7 | Topic | Amoxicillin | "Amoxicillin/administration and dosage"[Mesh] | Intervention/ Substance |
| #8 | Topic | Amprolium | "Amprolium/administration and dosage"[Mesh] | Intervention/ Substance |
| #9 | Topic | Apramycin | "apramycin" [Supplementary Concept] | Intervention/ Substance |
| #10 | Topic | Chlortetracycline | "Chlortetracycline/administration and dosage"[Mesh] | Intervention/ Substance |
| #11 | Topic | Colistin | "Colistin/administration and dosage"[Mesh] | Intervention/ Substance |
| #12 | Topic | Doxycycline | "Doxycycline/administration and dosage"[Mesh] | Intervention/ Substance |
| #13 | Topic | Florfenicol | "florfenicol" [Supplementary Concept] | Intervention/ Substance |
| #14 | Topic | Flumequine | "flumequine" [Supplementary Concept] | Intervention/ Substance |
| #15 | Topic | Lincomycin | "Lincomycin/administration and dosage"[Mesh] | Intervention/ Substance |
| #16 | Topic | Neomycin | "Neomycin/administration and dosage"[Mesh] | Intervention/ Substance |
| #17 | Topic | Spectinomycin | "Spectinomycin/administration and dosage"[Mesh] | Intervention/ Substance |
| #18 | Topic | Sulfonamide* | "Sulfonamides/administration and dosage"[Mesh] | Intervention/ Substance |
| #19 | Topic | Tetracycline | "Tetracycline/administration and dosage"[Mesh] | Intervention/ Substance |
| #20 | Topic | Oxytetracycline | "Oxytetracycline/administration and dosage"[Mesh] | Intervention/ Substance |
| #21 | Topic | "Oxolinic Acid" | "Oxolinic Acid/administration and dosage"[Mesh] | Intervention/ Substance |
| Set | Field | Search String | MeSH terms | Concepts/Key Elements |
|-----|-------|---------------|------------|-----------------------|
| #22 | Topic | Paromomycin   | "Paromomycin/administration and dosage" [Mesh] | Intervention/Substance |
| #23 | Topic | “Penicillin V” | "Penicillin V/administration and dosage" [Mesh] | Intervention/Substance |
| #24 | Topic | Tiamulin      | "tiamulin" [Supplementary Concept] | Intervention/Substance |
| #25 | Topic | Thiamphenicol | "Thiamphenicol/administration and dosage" [Mesh] | Intervention/Substance |
| #26 | Topic | Tilmicosin    | "tilmicosin" [Supplementary Concept] | Intervention/Substance |
| #27 | Topic | Trimethoprim  | "Trimethoprim/administration and dosage" [Mesh] | Intervention/Substance |
| #28 | Topic | Tylosin       | "Tylosin/administration and dosage" [Mesh] | Intervention/Substance |
| #29 | Topic | Valnemulin    | "valnemulin" [Supplementary Concept] | Intervention/Substance |
| #30 | Topic | Tylvalosin    | "tylvalosin" [Supplementary Concept] | Intervention/Substance |
| #31 | Topic | Feed          | "Animal Feed" [Mesh] | Intervention/Route |
| #32 | Topic | additive OR additives | "Food Additives" [Mesh] | Intervention/Route |
| #33 | Topic | Water         | "Water" [Mesh] | Intervention/Route |
| #34 | Topic | #1 OR #2 OR #3 OR #4 OR #5 OR #6 | | |
| #35 | Topic | #31 OR #32 OR #33 | | |
| #36 | Topic | #34 AND #7 AND #35 | | |
| #37 | Topic | #34 AND #8 AND #35 | | |
| #38 | Topic | #34 AND #9 AND #35 | | |
| #39 | Topic | #34 AND #10 AND #35 | | |
| #40 | Topic | #34 AND #11 AND #35 | | |
| #41 | Topic | #34 AND #12 AND #35 | | |
| #42 | Topic | #34 AND #13 AND #35 | | |
| #43 | Topic | #34 AND #14 AND #35 | | |
| #44 | Topic | #34 AND #15 AND #35 | | |
| #45 | Topic | #34 AND #16 AND #35 | | |
| #46 | Topic | #34 AND #17 AND #35 | | |
| #47 | Topic | #34 AND #18 AND #35 | | |
| #48 | Topic | #34 AND #19 AND #35 | | |
| #49 | Topic | #34 AND #20 AND #35 | | |
| #50 | Topic | #34 AND #21 AND #35 | | |
| #51 | Topic | #34 AND #22 AND #35 | | |
| #52 | Topic | #34 AND #23 AND #35 | | |
| #53 | Topic | #34 AND #24 AND #35 | | |
| #54 | Topic | #34 AND #25 AND #35 | | |
| #55 | Topic | #34 AND #26 AND #35 | | |
| #56 | Topic | #34 AND #27 AND #35 | | |
| #57 | Topic | #34 AND #28 AND #35 | | |
| #58 | Topic | #34 AND #29 AND #35 | | |
MeSH terms were used in Medline.

2.3.2. Language

The search was performed exclusively in English.

2.3.3. Time period

No time limits were applied in the literature search. The last update to each database and the search date were recorded in the raw data and final report.

2.2. Search areas

2.3.1. Electronic bibliographic databases

Two multi-disciplinary/large databases (Scopus and Web of Science Core Collection) as well as four more specialist/subject-specific databases (AGRICOLA, AGRIS, CABI - Animal Health & Production Compendium, and MEDLINE) were searched (EFSA, 2010; Wood et al., 2018). These databases were selected based on the proposals given by Glanville et al. (2014) and on their coverage of scientific literature for relevant subjects including, but not limited to, medicine, pharmacology, animal health, food and feed. The document types in these databases include journal articles, bulletins, dissertations, conference proceedings, books, monographs, reports, theses and articles in press.

2.3.2. Internet searches

The search in electronic bibliographic databases were complemented with internet searches (checking the relevance of the first 100 results in Google and Google Scholar) to identify potentially relevant studies outside electronic bibliographic databases and to mitigate effects of publication bias. We explicitly looked for information in PhD theses, expert opinions and authority assessments on use levels of the antimicrobials for promoting growth or increasing yield.

2.3.3. Manual searches

If any reviews or scientific opinions from regulatory agencies were retrieved using the intervention/exposure specific search terms, then the reference list from those records were manually searched for new records that met the eligibility/inclusion criteria.

If any influential study were identified, all studies citing this key study were checked for relevance.

2.3. Study selection

2.3.1. Process

The process of selecting relevant studies were conducted in two stages (EFSA, 2010).

- Stage 1: Rapid assessment of title and abstract of studies. Those records that were clearly irrelevant were excluded from further review, while records that were relevant or had unclear relevance were reviewed in Stage 2.
- Stage 2: Detailed assessment of full-text documents. An explanation was provided for any records that are deemed irrelevant in Stage 2 and these were excluded from further review. Any relevant records identified in Stage 2 were summarized and subjected to reliability assessment and evaluation of the implications of the record on the food and feed or environmental risk assessments.

2.3.2. Quality assurance

Two independent reviewers reviewed the records for inclusion/exclusion. Reviews were kept independent by keeping selections private at each stage of the review process. Reviewers scored the
records as either 1) relevant or of unclear relevance, or 2) clearly irrelevant. During the rapid assessment process (Stages 1), only records that were deemed clearly irrelevant by both reviewers were excluded from further review. This conservative approach ensured that all potentially relevant records were evaluated until they were deemed to be either relevant or clearly irrelevant in Stage 2.

If there was a disagreement between the reviewers regarding the relevance for a particular record at Stage 2 then an additional reviewer was brought in as a tie breaker. Considering the tie breaker’s opinion, the majority position of relevance on the record was the agreed position.

2.3.3. Eligibility/inclusion criteria to establish relevance

Table 4 summarizes eligibility/inclusion criteria for establishing relevance of retrieved records and provides high level key concepts for inclusion/exclusion.

| Concepts                  | Criteria                        | Comment                                                   |
|---------------------------|---------------------------------|-----------------------------------------------------------|
| Population                | food producing animals          | The relevant species are listed in Error! Reference source not found. |
| Intervention/Substance    | 24 antimicrobials               | The relevant substances are listed in Error! Reference source not found. |
| Intervention/Route        | oral administration             | Studies that address the medication via feed or water.    |
| Intervention/Level        | use levels/dosages              | Studies that specify use levels/dose-response relationships |
| Comparator                |                                 | Negative/ positive control group, different levels of application |
| Outcomes                  | effects on feed intake, feed efficiency | Studies that address use of antibiotics in livestock to promote growth/yield/health in general. |
| Information/data requirements | Use level, dosage, effects | Studies that potentially contribute to the knowledge about levels of antimicrobials that have a growth promotion/production yield increase effect can be seen as relevant using this criterion. Studies addressing issues such as benefits, socioeconomics, ethics, prevention/treatment of bacterial infections, analytical methods, public perception and risk communication were excluded using this criterion. |
| Access                    | Full text document              | If potentially relevant full-text documents were not obtained, then they were listed in a table with a description of the (unsuccessful) methods that have been used to try to obtain a copy |
| Reporting format          | Papers presenting original data | Records that do not present original/primary data (e.g. reviews, editorials, position papers) were excluded. Reviews were only included if they presented data that were not available from a primary research study. |
| Reporting format          | Duplicate studies               | Duplicate studies were excluded at the initial screening stage and only one copy was presented |

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