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LCI METHODOLOGY AND DATABASES

Characterizing antibiotics in LCA—a review of current practices and proposed novel approaches for including resistance

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Abstract

Purpose With antibiotic resistance (ABR) portrayed as an increasing burden to human health, this study reviews how and to what extent toxicological impacts from antibiotic use are included in LCAs and supplement this with two novel approaches to include ABR, a consequence of antibiotic use, into the LCA framework.

Methods We review available LCA studies that deal with toxicological aspects of antibiotics to evaluate how these impacts from antibiotics have been characterized. Then, we present two novel approaches for including ABR-related impacts in life cycle impact assessments (LCIAs). The first approach characterizes the potential for ABR enrichment in the environmental compartment as a mid-point indicator, based on minimum selective concentrations for pathogenic bacteria. The second approach attributes human health impacts as an endpoint indictor, using quantitative relationships between the use of antibiotics and human well-being.

Results and discussion Our findings show that no LCA study to date have accounted for impacts related to ABR. In response, we show that our novel mid-point indicator approach could address this by allowing ABR impacts to be characterized for environmental compartments. We also establish cause-effect pathways between antibiotic use, ABR, and human well-being that generate results which are comparable with USEtox and most endpoint impact assessment approaches for human toxicology.

Conclusions Our proposed methods show that currently overlooked impacts from ABR enrichment in the environment could be captured within the LCA framework as a robust characterization methodology built around the established impact model USEtox. Substantial amounts of currently unavailable data are, however, needed to calculate emissions of antibiotics into the environment, to develop minimum selective concentrations for non-pathogenic bacteria, and to quantify potential human health impacts from AB use.

Keywords Antibiotics · LCA · Resistance · AMR · Antimicrobials · Human health impacts · Resistance · Toxicology · USEtox

1 Introduction

Antibiotic (AB) substances are used for treating bacterial infections by killing or inhibiting growth of these organisms (Davies and Davies 2010; Kümmerer 2009). The term AB is broad and

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envelops hundreds of different compounds, of which close to 300 are classified as important for human medicine and are categorized into 30 + groups according to their origin and mode of action (World Health Organization 2019). ABs have become our primary tool for treating and preventing the proliferation of pathogenic bacterial diseases in a wide range of settings, including human medicine, livestock (van den Bogaard and Stobberingh 1999), and aquaculture farms (Sapkota et al. 2008), as well as in agriculture to control for bacterial diseases in plants (Stockwell and Duffy 2012). They are the primary treatment for pneumonia, tuberculosis and gastrointestinal infections, diseases that historically are thought to have been responsible for 30% of all human deaths, but they are also essential for post-surgical care (Fair and Tor 2014). Inappropriate use of ABs and their environmental release may, however, result in negative consequences (in a concentration dependent context) in the environmental compartment as they can: (a) infer toxic effects on several living organisms (Carlsson et al. 2009) and (b) modify microbial community compositions and affect ecological functions (Costanzo et al. 2005; Grenni et al. 2018). Additionally, negative effects to humans include: (c) indiscriminately killing both pathogenic and non-pathogenic bacteria, including bacterial communities that fill useful biological functions (Jernberg et al. 2010; Lange et al. 2016); (d) induce side effects in humans (Wypych and Marsland 2018); and (e) promote the development of antibiotic resistant genes (Jernberg et al. 2010; Pérez-Cobas et al. 2013).

Of the abovementioned impacts, antibiotic resistance (ABR) development in pathogenic bacteria is seen as the most foreboding for human wellbeing, due to the central role of ABs in modern medicine (World Health Organization 2014). Bacteria can develop resistance to ABs either through mutations or by acquisition of resistance genes from other bacteria through different modes of horizontal gene transfer even at low concentrations (i.e., ng/L to few µg/L; Cabello 2006; Grace 2015; Bengtsson-Palme and Larsson 2016; Jutkina et al. 2018; Klein et al. 2018).

ABR genes have existed for millennia (D'costa et al. 2011), but the current use of tens of thousands of tonnes of ABs each year has resulted in substantial releases of ABs into the environment (Van Boeckel et al. 2015; Robinson et al. 2016), thereby generating large areas for interactions between ABs and bacteria which can lead selection for AB resistance genes in environmental bacteria (Cabello 2006; Mathew et al. 2007; Rizzo et al. 2013; Larsson 2014; Xiong et al. 2015; Cabello et al. 2016; Chuah et al. 2016; Larsson et al. 2018; Osman et al. 2018). There is a growing body of literature connecting ABs released into the environment with the development of ABR in bacterial communities (Heinemann 1999; Wright 2007; Larsson 2014) and an increased frequency of ABR genes in environmental compartments (Finley et al. 2013), yet the links between environmental ABR bacteria and the impacts to human health are not fully understood. The collection of genes coding for ABR present in the environment can be viewed as a pool of available genetic material which can be transferred between bacteria and is commonly referred to as "the resistome" (D'Costa et al. 2006; Wright 2007; Surette and Wright 2017). Models have been developed for correlating anthropogenic AB emissions and the resistance development in the environment based on abiotic parameters (Amos et al. 2015), as well as relationships between AB use in food animal production and human exposure to ABR pathogens (van Bunnik and Woolhouse 2017). Nonetheless, it remains difficult to establish useful dose-response relationships between AB use and the associated impacts, since causalities between AB use, resistance development, and transmission are difficult to pinpoint (Price et al. 2015).

Despite the overwhelming human health benefits gained from using pharmaceuticals like ABs, it is imperative to assess the negative impacts from emissions of these substances to better improve regulation and manage impacts. Life cycle assessment (LCA), among other environmental frameworks, has been used to assess impacts related to the use of ABs. LCA details the environmental impacts related to a product's or service's life cycle. In LCA, human and ecosystem impacts from the release of chemicals are generally captured by toxicological impact categories. Most of these toxicological impact assessment methodologies build upon available laboratory toxicity data and extrapolation methods assigning fate, effect, and exposure pathways to chemical agents. Depending upon scope, freshwater ecotoxicity, marine ecotoxicity, and/or cancer and non-cancer-related human toxicity (European Commission 2010) are either estimated at an intermediary point in the underlying impact pathway by midpoint indicators (e.g. number of cancer or non-cancer disease cases in humans or potentially affected fraction of species in the aquatic environment; PAF m^3 kg^{-1}), or at the end of the impact pathway as endpoint indicators (e.g. disability adjusted life-years (DALY) or potentially disappeared fraction of species to change in concentration (PDF m^3 kg^{-1}) (Hauschild and Huijbregts 2015).

In this study, we first review (Sec. 3.1) how impacts from AB use and ABR have been characterized among published LCAs. We then propose two novel impact characterization models to capture ABR in LCA (Sec. 3.2) and discuss their respective strengths and weaknesses. Conclusively (Sec. 4), we summarize the outcomes to suggest best practices for AB use in LCA.

2 Methodology

2.1 Review of AB use in LCA literature

Relevant literature on previous LCA studies incorporating AB or pharmaceuticals was screened using web of science on 10 March 2021. The search used the phrase "TS = ("LCA" OR "LCIA" OR "life cycle assessment" OR "life cycle analysis" OR "life cycle inventory assessment" OR USEtox) AND TS = (antimicr* OR antibio* OR pharmaceutical* OR micropoll*))" while delimiting the search to English-language articles

spanning the years 2008–2020. Search denominators and methodology overview is given in the supplementary information (Fig. S1). The search generated 266 articles that were targeted for screening, of which 80 passed a title screening. Another 37 were rejected following abstract screening. Of remaining 43 articles read in full, 27 did not characterize ABs and were excluded. Thus, 16 articles are included in the review, with the addition of the study by Henriksson et al. (2015) that had been identified prior to screening, and are summarized in Table 1. Figures were designed using RStudio, Inc, Version 1.1.423 and Microsoft PowerPoint 2016.

2.2 Proposing novel approaches to include ABR in LCA

Potential impacts of ABs reaching the environment are separated between toxicological impacts and resistance development. Toxicological impacts can be captured in the current toxicological impact model USEtox, applying a three-step approach to derive characterization factors (CFs) for toxic substances applied in the LCA, considering fate, exposure, and effect data (Fantke et al. 2017; Rosenbaum et al. 2011).

Table 1 Overview of articles reviewed that considerer AB toxicity (both human toxicity and ecotoxicity) in LCA studies

Author	Year	System	LCIA methodology (for ecotoxicity)	Midpoint/endpoint characterization	Number of new AB CFs calculated	Ecotoxicity database (for antibiotics)
Munoz et al.	2008	WWTP	EDIP97 and USES 2.0	Both	7	USEPA Ecotox database[a]
Munoz et al.	2009	WWTP	EDIP97 and USES 2.0	Both	0	USEPA Ecotox database[a]
Hospido et al.	2010	WWTP	CML 2 baseline 2000	Midpoint		Muñoz et al. 2008
Stone et al.	2010	Swine farming	USES-LCA 2.0	Both	0	-
Stone et al.	2011	Swine farming	EcoIndicator 99	Endpoints	0	-
Igos et al.	2012	WWTP	EDIP97, EDIP2003, and ReCiPe + USEtox	Endpoint (EDIP2003), Midpoint (USEtox)	0	Wikipharma[b] and USEPA Ecotox database (ECOSAR)
Morais et al.	2013	CFs	USEtox	Midpoint	6	ECOTOX database 4.0[c]
Igos et al.	2013	WWTP	EDIP2003 and USEtox	Endpoint (EDIP2003), Midpoint (USEtox)	0	Wikipharma[b] and USEPA Ecotox database (ECOSAR)
Alfonsin et al.	2014	CFs	USES-LCA 2.0 and USEtox	Midpoint (both USES-LCA & USEtox)	4	USEtox, various literature[d]
Henriksson et al.*	2015	Aquaculture	USEtox	Midpoint	24	various literature[e], USEPA ECOTOX database[a]
Lorenzo-Toja et al.	2016	WWTP	USES-LCA 2.0	Both	0	Alfonsín et al. 2014
Ortiz de Garcia et al.	2017	CFs	USEtox	Midpoint	7	USEPA Ecotox database[a], various literature[f]
Tarpani et al.	2018	WWTP	USEtox	Midpoint	0	Alfonsín et al. 2014
Rahman et al.	2018	WWTP	USEtox	Midpoint	0	USEtox, Alfonsín et al. 2014
Emara et al.	2018	CFs	USEtox, EDIP 97, and USES-LCA	Both	0	USEPA Ecotox database[a], Wikipharma[b], TOXLINE database[f], USEtox
Li et al.	2019	WWTP	USEtox	Midpoint	11	RIVM e-toxBase[g], USEtox
Tarpani et al.	2020	WWTP	USEtox	Midpoint	0	Alfonsín et al. 2014

*Study acknowledged prior to review, not captured by the literature screening.

[a]http://cfpub.epa.gov/ecotox/

[b]http://www.wikipharma.org

[c]ECOTOX Database Release 4.0, US Environmental Protection Agency, 2007

[d]Barceló and Petrovic, 2011; Fent et al., 2006; Isidori et al., 2005; Santos et al., 2010

[e]Rico et al., 2013; Rico and Van den Brink, 2014

[f]Dobbins et al., 2009; Iannacone and Alvariño, 2009; Ortiz de García et al., 2014; Santos et al., 2010; Terasaki et al., 2009

[g]https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm

[h]www.e-toxbase.com (not accessible 2020-09-17). WWTP= wastewater treatment plants; CFs = characterization factors

For impacts related to resistance development, we choose to target: (1) ABR development in the environment as a mid-point indicator by sourcing effect data related to concentrations of ABs where resistance development can occur based on the risk assessment methodology developed by (Rico et al. 2017), and (2) human health impacts as a result from AB use by suggesting a linear dose-response model based on statistical correlation connecting AB use, resistance development and human health impacts. This was accomplished by sourcing data from veterinary and medical literature while limiting the scope to the EU due to data scarcity.

3 Results and discussion

3.1 Findings of the review

Seventeen LCA-related articles deal with ABs, of which two consider indirect toxic impacts related to AB production and transportation (Stone et al. 2010, 2011), three calculate freshwater ecotoxicity CFs for ABs and use them in LCAs (Muñoz et al. 2008; Henriksson et al. 2015; Li et al. 2019), two only calculate CFs for ABs (Alfonsín et al. 2014; Ortiz de García et al. 2017) and eight use available CFs for ABs to conduct LCAs (Muñoz et al. 2009; Hospido et al. 2010; Igos et al. 2012, 2013; Lorenzo-Toja et al. 2016; Rahman et al. 2018; Tarpani and Azapagic 2018; Tarpani et al. 2020). Meanwhile, Morais et al. (2013) compare the uncertainty and variability of characterization results at various pH using the USEtox scientific consensus model V1.01 (Rosenbaum et al. 2008), and Emara et al. 2018 compare AB-related CFs using different impact assessment methodologies. An overview of reviewed articles is presented in Table 1. The articles were published from 2008 and onwards, the same year as the USEtox consensus model was developed. Of the thirteen studies that carried out life cycle inventory assessments (LCIAs), ten evaluated wastewater treatment plant interventions and three animal farming. The two studies by Munoz et al. (2008, 2009) use both EDIP 97 (Potting and Hauschild 2006) and USES-LCA (Huijbregts et al. 2000) for LCIA, with EDIP 97 and USES-LCA 2.0 characterization methodologies respectively thereby characterizing impacts at both mid-point and endpoint. Stone et al. (2010) use ReCiPe 2008 (Goedkoop et al. 2013) that promotes USES-LCA 2.0 characterization methodology for toxicological impacts. Meanwhile, Stone et al. 2011 use EcoIndicator99 v2.06 (Goedkoop and Spriensma 2001) and Igos et al. (2012) EDIP 97 and EDIP 2003, as well as ReCiPe 2008 combined with USEtox. Igos et al. (2013) use EDIP2003 and ReCiPe 2008 combined with USEtox. Hospido et al. (2010) declares using CLM 2 baseline 2000 for midpoint impact assessment (Guinée et al. 2002). Henriksson et al. (2015), Tarpani and Azapagic (2018), and Tarpani et al. (2020) all characterize freshwater ecotoxicity using USEtox V1.01, while Lorenzo-Toja et al. (2016) characterize emissions using USES-LCA 2.0. The two last studies, Rahman et al. (2018) and Li et al. (2019), perform LCIA with TRACI 2.1, where USEtox is the proposed toxicological characterization methodology. Four studies deal with more than one toxicological characterization method as the focus of these studies is to evaluate characterization results or LCIA methodologies rather than performing LCAs.

Overall, the scope and methodologies vary substantially among studies, as do calculated CFs for ABs. Eleven studies apply USEtox methodology for impact characterizations, of which four establish CFs and seven carry out full LCAs. Among these, Alfonsín et al. (2014) characterize four ABs for both USEtox and USES-LCA. Lorenzo-Toja et al. (2016) utilize these USES-LCA CFs, while Tarpani and Azapagic (2018) and Tarpani et al. (2020) use the USEtox CFs from Alfonsín et al. (2014) for LCAs of wastewater treatment plants (WWTPs). Muñoz et al. (2008) rank the toxicity for 97 pollutants, create seven new CFs for antibiotics, and apply these in an LCA of WWTP. These CFs are subsequently used by Muñoz et al. (2009) and Hospido et al. (2010) in other LCAs of WWTPs. Henriksson et al. (2015) and Li et al. (2019) also generate novel CFs for ABs using the USEtox methodology (V1.01 and V2.0 respectively) and use them for their respective LCAs. Meanwhile, Morais et al. (2013) investigate how pH variation influence USEtox fate modelling of agents and create novel CFs for six ABs. Ortiz de García et al. (2017) calculate CFs for seven additional ABs, and Emara et al. (2018) compare available impact assessment methodologies and CFs for ABs and other agents.

Of the six studies generating novel freshwater ecotoxicity CFs for ABs, five present fate, exposure, and effect factors in their respective supplementary information. Two of these (Henriksson et al. 2015; Ortiz de García et al. 2017) also detail AB's source toxicity data, but derive their effect factors somewhat differently. Ortiz de García et al. (2017) prioritized chronic toxicity data, as recommended by Fantke et al. (2017), while Henriksson et al. (2015) use both acute and chronic toxicity data.

To date, 40 antibiotic agents have been characterized for freshwater ecotoxicity impact with the USEtox methodology (Fig. 1; data available in supplementary information, Table S1). For some ABs that were characterized more than once, large variations exist (e.g. 3.2E + 1 PAF m^3 per day and kg emitted^{-1} to 1.06E + 7 PAF m^3 per day and kg emitted Amoxicillin), while 24 out of 40 antibiotics only were characterized once.

Despite novel contributions of AB CFs using USEtox, only 40 of the over 300 ABs deemed critically important for human medicine have been characterized for freshwater ecotoxicity (Fantke et al. 2017; World Health Organization 2019).

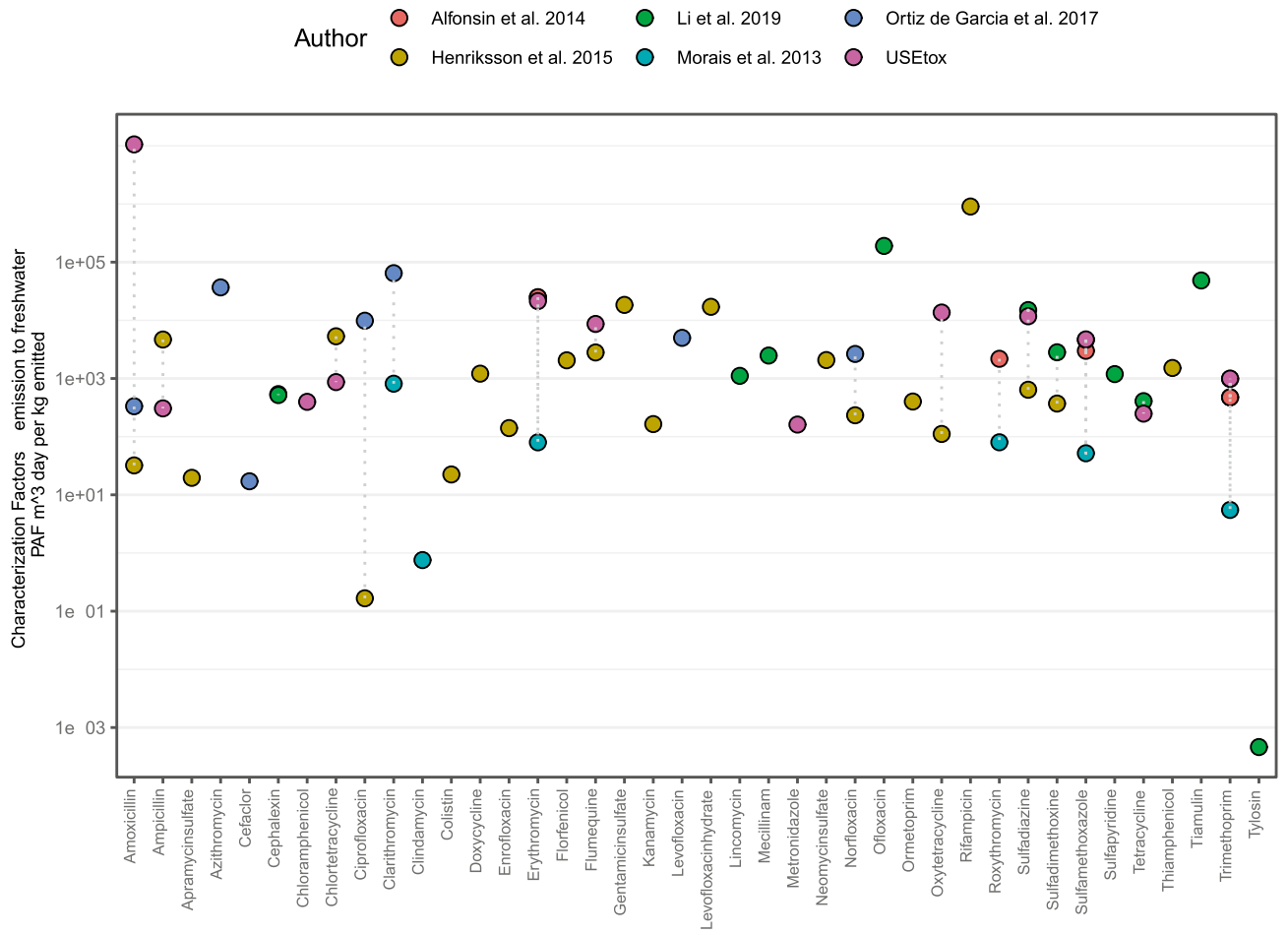


Fig. 1 Available CFs for AB emissions to freshwater calculated using USEtox, FETP = freshwater ecotoxicity potential. Units are presented in PAF m^3 day kg^{-1} emitted

Moreover, the USEtox V2.01 database presents 23 readily available human health impacts for ABs, but only four of these have CFs for human toxicity attributed, the rest are defined as either "*n.a*" or "0", which implies toxicity data are labelled as "neglected" (USEtox® organic substances database 2.01 [built 10-July-2017]). An additional nine ABs are characterized for human health impacts among the reviewed studies (see Table 2 based on data from Emara et al. 2018). The CFs from Ortiz de García et al. (2017) are reported as "human toxicity potential – total" (an aggregation of both carcinogenic and non-carcinogenic impact), yet the toxicological input data label all of the characterized ABs as non-carcinogenic (NC) and they are therefore labelled as HTP-NC in Table 2.

To summarize, the use of ABs and the environmental release of AB residues may result in ecotoxicological impacts on animals and humans, changes in microbial communities in ecosystems and humans, and resistance development. Ecotoxicological impacts are addressed in several LCA studies using different LCIA methodologies. Most of the reviewed studies look at freshwater ecotoxicity using USEtox, but conclude up to six orders of magnitude difference in CFs for some ABs. The cause for inconsistencies in freshwater ecotoxicity CFs remains unclear since the underlying toxicity data used for calculating the effect factors remain unavailable. However, Morais et al. (2013) show that CFs are sensitive to differences in abiotic degradation rates as well as ecotoxicological effect (EC50) data, which generally are sourced from different empirical experiments, as no standardized database for such data is available for ABs. Nonetheless, the chemical properties and experimental data on ABs that support the CFs remain inconsistent across literature. Greater efforts are therefore needed towards generating further modelling and experimental data for some compounds, as well as completing and harmonizing datasets of toxicological properties that could support effect factors to yield robust CFs.

Based on our review, we conclude that the most severe knowledge gaps include the evaluation of potential human health impacts pathways from AB use, resistance development in the environment, and human health impacts associated to ABR. Four LCA studies included impacts from ABs on human health, but no LCA study to date that is assessing potential human health impacts has tried to capture the consequences

Table 2 Human toxicity potential characterizations available for ABs created with the USEtox method. Units are reported as "cases per kg emitted". HTP-C: human toxicity potential: carcinogenic, HTP-NC: human toxicity potential: non carcinogenic

Antibiotic	Source	Toxicity type	Emission to freshwater	Emission to seawater	Emission to natural soil	Emission to agricultural soil	Emission to urban air	Emission to rural air
Metronidazole	USEtox	HTP-C	3.30E−07	6.52E−11	1.14E−07	2.98E-07	5.40E-07	4.81E-07
Sulfamethazine	USEtox	HTP-C	1.08E−07	2.31E−11	2.69E−10	1.45E-09	6.48E-08	4.48E-08
Amoxicillin	Ortiz de Garcia 2017	HTP-NC	2.11E−08	4.84E−12	2.74E−09	4.50E-09	1.75E-08	1.80E-08
Azithromycin	Ortiz de Garcia 2017	HTP-NC	6.11E−06	2.10E−08	1.76E−07	9.44E-07	4.60E-06	4.72E-06
CEFACLOR	Ortiz de Garcia 2017	HTP-NC	1.54E−08	3.17E−12	2.06E−09	3.02E-09	1.24E-08	1.28E-08
Ciprofloxacin	Ortiz de Garcia 2017	HTP-NC	1.13E−07	2.51E−11	4.46E−08	6.17E-08	1.11E-07	1.15E-07
Clarithromycin	Ortiz de Garcia 2017	HTP-NC	3.14E−07	1.21E−09	8.60E−08	1.95E-07	2.92E-07	3.01E-07
Levofloxacin	Ortiz de Garcia 2017	HTP-NC	2.51E−06	6.45E−10	1.20E−06	1.41E-06	2.17E-06	2.26E-06
Norfloxacin	Ortiz de Garcia 2017	HTP-NC	3.05E−07	6.17E−11	1.09E−07	1.28E-07	1.20E-07	1.25E-07
Sulfamethoxazole	Alfonsin 2014	HTP-NC	1.58E−07	1.04E−10	1.03E−08	1.70E-08	3.24E-08	7.03E-09
Sulfamethoxazole	USEtox	HTP-NC	4.70E−07	1.45E−10	1.21E−07	4.35E-07	1.28E-07	7.84E-08
Trimethoprim	Alfonsin 2014	HTP-NC	5.66E−07	1.54E−10	2.29E−08	3.66E-08	9.16E-08	2.39E-08
Trimethoprim	USEtox	HTP-NC	2.78E−06	7.67E−10	3.67E−08	3.18E-07	5.64E-07	2.84E-07

of ABR. So far the only impacts considered are direct toxicity without addressing ABR, which is briefly mentioned by Igos et al. (2012) and Emara et al. (2018). As described by Ashbolt et al. (2013), resistance genes which propagate in the environment and become a human health issue adhere to different pathways than ecotoxicological impacts and will therefore require a different impact assessment approach. Since ABs act as a causative agent for ABR development, spread of resistant bacteria can subsequently occur in the environment and be transmitted to humans. Both latter steps cannot be assessed through physiochemical fate models because bacteria are the main carriers of these resistance genes and they propagate through complex biological interactions. As such, disease transmission and subsequent impacts on human health are not assessed using the exposure and effect pathways currently included in the USEtox model (Eq. 1). Without relevant pathways to capture the extent of ABR impacts, these are possibly greatly underestimated in LCAs.

3.2 Two proposed approaches for addressing ABR in LCA

Since no cause-effect pathway exists for the impacts of ABR development in LCIA methodology, we below present two novel approaches that could potentially allow for ABR impacts to be quantified using causal relationships: (1) the use of minimum selective concentration (MSC) distributions to characterize ABR enrichment in the environment as a midpoint impact; and (2) the correlation between ABs used on regional scale with human health impacts caused by ABR, quantified as DALYs per kg of AB used as an endpoint impact.

The first approach, modelling of ABR enrichment in the environment, uses the USEtox® methodology as a starting point, as it is the framework recommended by both the Society of Environmental Toxicology and Chemistry (SETAC) and the Joint Research Centre (European Commission 2010). In USEtox, *Fate factors* capture the physiochemical properties of agents and predict their estimated distribution in environment compartments; *exposure factors* calculate bioavailability to aquatic organisms or exposure pathways for humans, while *effect factors* benchmark the actual toxicity of a compound, generally based upon laboratory studies (Eq. 1 describes human impact characterization and Eq. 3 describes ecotoxicological characterization).

$$\begin{aligned} \textit{Characterization factor} = \textit{Fate factor}\left(\frac{\mathrm{kg}_{\textit{ in compartment}}}{\frac{\mathrm{kg}_{\textit{ emitted}}}{\mathrm{day}}}\right) \\ \times \textit{Exposure factor}\left(\frac{\frac{\mathrm{kg}_{\textit{ intake}}}{\mathrm{day}}}{\mathrm{kg}_{\textit{ in compartment}}}\right) \\ \times \textit{Effect factor}\left(\frac{\text{disease cases}}{\mathrm{kg}_{\textit{ emitted}}}\right) \end{aligned} \quad (1)$$

Again, this approach is aimed at capturing toxicological effects of ABs, and does not prescribe how to incorporate ABR impacts.

3.2.1 Approach 1: characterizing ABR enrichment in the environment (mid-point)

Approach 1 attempts to quantify the enrichment of resistance genes in environmental bacteria based on environmental fate models for ABs and theoretical minimum selective concentration (MSC) distributions as a mid-point impact, similar to USEtox's ecotoxicity impacts.

The proposed characterization model is based on the methodology developed by Rico et al. (2017), where MSCs are inferred from minimum inhibitory concentrations (MIC) for pathogenic bacteria obtained from the EUCAST database (European Committee on Antimicrobial Susceptibility Testing 2020). In their study, MSCs were extrapolated from MICs by applying a flat extrapolation factor of 10. These extrapolation factors are derived as the mean MIC/MSC ratio obtained in experimental studies (Gullberg et al. 2011; Liu et al. 2011), but refinements of this extrapolation factor should be implemented as soon as further experimental or modelling data become available. Such improvements should account for differences between broad-spectrum and selective antibiotics, considering their mode of action in bacteria.

MSC data for each antibiotic are used to fit normal distributions to the log-transformed MSC data, similarly to the species sensitivity distribution approach used in ecotoxicological impact characterization (Posthuma et al. 2001). In an analogous manner, the MSC distributions could be used to extrapolate the hazardous concentration that will promote the development of ABR in 50% of bacteria (HC_{50}), which can be calculated as the geometric mean of the MSC data. A difference to ecotoxicity characterization methodology in USEtox is that HC_{50} values are generated from the geometric mean of chronic EC_{50} or LC_{50} values (effect concentration for 50% of tested organisms and lethal concentration of 50% of tested organisms respectively) for aquatic organisms from several trophic levels (Fantke et al. 2017). A chronic endpoint is preferred as the chemical fate and exposure calculations are performed following a steady-state approach, so estimated environmental concentrations resemble chronic exposure (Guinée and Heijungs 1993). The use of EC_{50} or LC_{50} values, as opposed to a no observed effect concentration (NOEC) or lowest observed effect concentration (LOEC), is mainly supported by the statistical robustness of the 50% response level (Crane and Newman 2000; Larsen and Hauschild 2007). In the proposed approach, the MSCs approximate the chronic resistance LOEC for bacteria, which are based on thousands of data points compiled in the EUCAST database rather than on a single dose-response experiment, so a sufficient statistical robustness is assumed for this value as representative for a given bacterial taxon. Furthermore, the number of bacteria that is included in the EUCAST database is large (> 8) for the most commonly used antibiotics (Bengtsson-Palme and Larsson 2016). Questionable is how representative the pathogenic bacteria included in the EUCAST database are for bacterial communities in the environment. In this regard, Bengtsson-Palme and Larsson (2016) demonstrate a weak link between taxonomic divergence and sensitivity to antibiotics, and the study by Tello et al. (2012) finds no significant difference in sensitivity between pathogenic bacteria that inhabit human bodies exclusively and those that have been reported to also inhabit environmental compartments. Thus, the EUCAST database presents itself as a useful proxy for estimating the susceptibility of environmental communities to antibiotic pressure.

Similarly to the formula established by Jolliet et al. (2003) for the effect factor calculation for ecotoxicity, the effect factor for ABR enrichment in environmental bacteria (EF_{ABR}) can be calculated as:

$$EF_{ABR} = \frac{0.5}{HC_{50}} \tag{2}$$

EF_{ABR}: ABR effect factor for a given environmental compartment e.g. freshwater ecosystems (PAF m^3 kg^{-1}).

HC_{50}: geometric mean of MSCs for bacteria (kg m^{-3}).

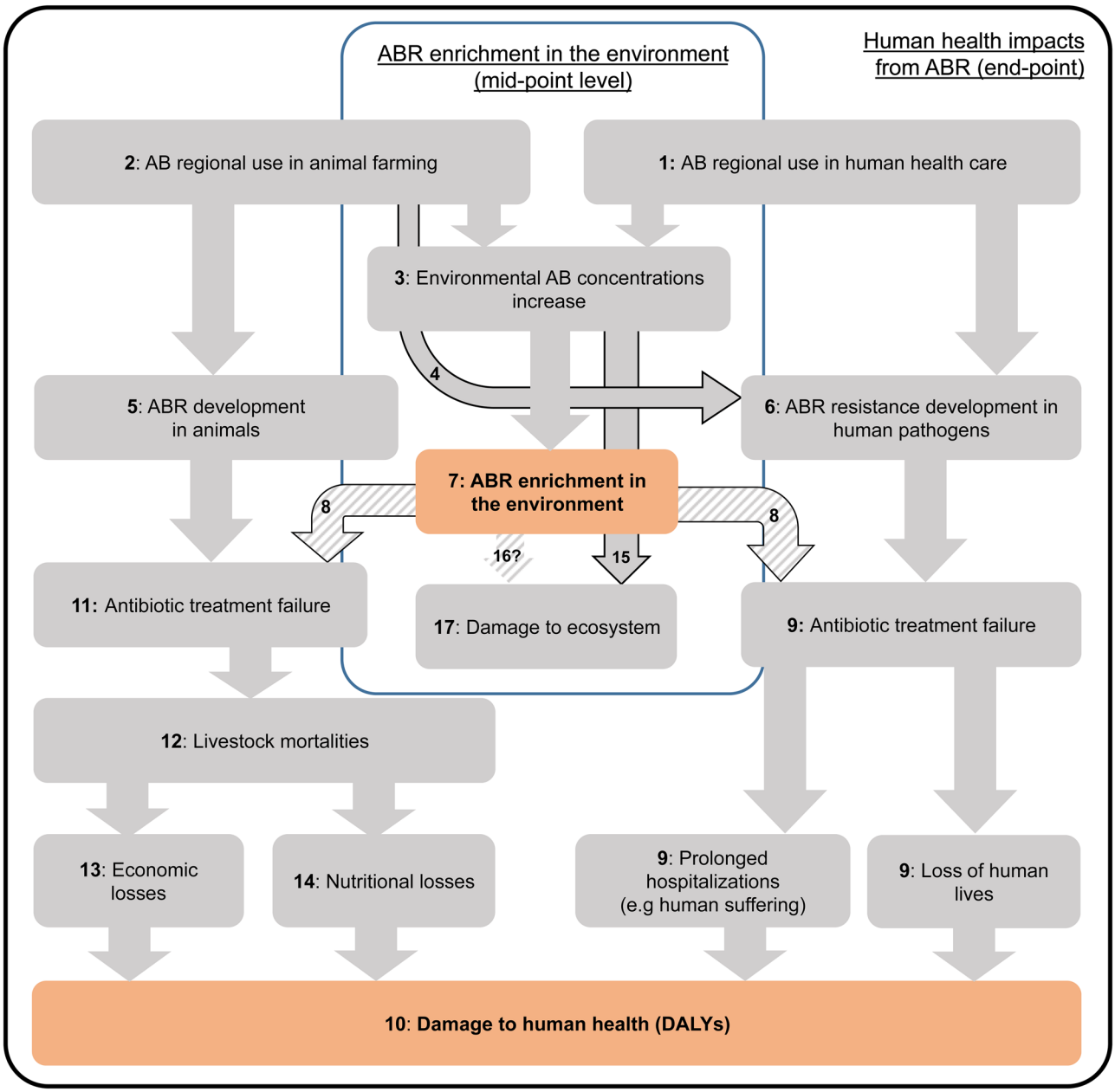
In ecotoxicity assessments, the effect factor relates to the change in PAF as a result of increases in contaminant concentration. In the proposed ABR enrichment assessment, this will refer to the change in the fraction of bacterial populations that acquire a significant increase of resistance genes due to a unit increase of AB exposure concentration. Analogous to the ecotoxicity assessment, it is based on a linear extrapolation from the HC_{50} down to HC_0 (slope of 0.5), and assumes that the acquisition of resistance at the community level increases with AB concentration.

Finally, the ABR characterization factor (PAF m^3 day per kg emitted) can be calculated as

$$\begin{aligned} CF_{ABR} = & Fate\ factor\left(\frac{\text{kg}_{\ in\ compartment}}{\frac{\text{kg}_{\ emitted}}{\text{day}}}\right) \\ & \times Exposure\ factor\left(\frac{\text{kg}_{\ bioavailable}}{\text{kg}_{\ in\ compartment}}\right) \\ & \times Effect\ factor\left(\frac{PAF\ m^3\ \text{day}}{\text{kg}_{\ emitted}}\right) \end{aligned} \tag{3}$$

where the fate factor describes the distribution of chemicals in the environment and the exposure factor describes the bioavailable fraction of chemicals that could cause harm to freshwater organisms (Fantke et al. 2017), thus utilizing the established modelling framework USEtox for characterizing distribution of ABs in the environment while only modifying the effect factor.

Following the methodology described above, ABR-HC_{50} values were generated for 14 ABs to replace ecotoxicological HC_{50} for USEtox input data (Table S5). The USEtox



calculations were set up in the USEtox® 2.1 [built 19-Oct-2017] interface software (available at https://usetox.org/), selecting freshwater emission ecotoxicity and applying default USEtox setting environment. ABR enrichment characterization factors could subsequently be generated in harmony with USEtox 2.1 (Table 3).

These results show that applying MSC-based HC_{50} values for ABs enables us to derive characterizations that fit the formerly established LCA framework, thereby complementing existing freshwater ecotoxicity impacts with ABR specific impacts. It should be clarified that the CFs generated by this model serve as comparative units of impact related to the resistance HC_{50} for bacteria at the community level, and not as a representation of resistance development dynamics following a concentration gradient, which could theoretically generate selection for resistance in bacteria at low concentrations, as well as remove resistance at high concentrations (e.g. killing bacteria). A strength of this approach is that all MIC data can be sourced from the EUCAST database, thus removing variations in HC_{50} values due to different data sourcing, as highlighted for ecotoxicological data above.

Finally, a point on the ecological relevance of this approach should be raised. The LCA framework accounts for emissions under steady-state conditions (Guinée and Heijungs 1993), while AB emissions can be influenced by pharmacokinetics and environmental processes, and

◂**Fig. 2** Impact pathway overview of AB from an LCIA perspective. (1) AB use data is reported as DDDs per 1000 inhabitants per day (DIDs) in respective EU country in the ECDC database (accessed 2020-09-19). (2) AB use data within the EU region reported as tonnes per year in (European Medicines Agency 2017). (3) Assessed with current fate models in USEtox. (4) No correlation between veterinary use of 3GC and resistance development in the human healthcare sector. (European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA) 2017). (5) Correlation between veterinary use of 3GC and resistance development in the food-animal sector. (European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA) 2017). (6) Correlation between human consumption of 3GC and resistance development in human health care sector. (European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA) 2017). (7) Proposed characterization factor in this paper, based on minimum inhibitory concentrations (MIC) of ABs; predictions of ABR development is used as a comparative endpoint. (8) Connecting the ABR present in the environmental compartment to AB treatment failure in the human and veterinary sector; no quantitative data is available for this pathway. (9) These steps are aggregated describing the effect to human health from resistance developed. (10) Cassini et al. (2019) assessment of treatment failure attributed to ABR can be found for the 16 most common pathogen-resistance combinations in Europe. Loss of human lives and prolonged hospitalizations as an effect are assessed within the same report. (11) No quantitative data available on impacts to veterinary medicine from ABR zoonosis. (12) No quantitative data available. (13) Innes et al. (2019) report an economic impact models from of enrofloxacin use and impacts from *Campylobacter*, *Salmonella*, and *E. coli* bacteria as externalities from AB use, which reaches US$ 2200 per kg enrofloxacin used. The model might accommodate calculations for 3GC in the EU as well. (14) A rational for establishing nutritional losses needs to be settled on. We would argue that there are highly variable regional differences across the world. In high-income regions, nutrients are easily substituted from another food source in contrast to low-income regions. However, antibiotic use strategies surely vary between small-holder animal husbandry and industrial-scale farming in the latter regions (no use vs. some use respectively). (15) Ecotoxicological modelling according to USEtox, damage to the ecosystem from increased AB concentrations in the environment is characterized as freshwater ecotoxicity impacts. (16) Weak evidence for damage to ecosystem from ABR (Eckert et al. 2019). (17) End-point measurement of ecotoxicological effects, no clear ecosystem effect from ABR

ABR development depend on the exposure level as well as on the exposure duration (Ashbolt et al. 2013). This implies that the applicability of this model serves better for systems with continuous emissions than systems with erratic AB use (e.g., WWTPs vs. aquaculture farms), but may be under-representing exposure scenarios that are prolonged in long periods. Additionally, events related to proliferation of resistance genes following ABR development, across species and exposure to humans, are not captured within this model. Such quantifications would be highly dependent on the exposure level and duration, and the bacteria present in the environment, which would need to account for more complex pathways. Connecting ABR enrichment in the environment to human health impacts (8 in Fig. 2) by incorporating other methods is currently being explored (Ashbolt et al. 2013; Ben et al. 2019), but is hampered by a lack of relevant data on how AB concentrations influence resistance development in human pathogenic bacteria and quantitative pathways describing environmental exposure to ABR. Hence, below we explore an alternative approach relating the use of ABs to human health impacts from ABR, which goes beyond the explanation of mechanistic relationships and the quantitative determination of each of these pathways.

Table 3 ABR enrichment CFs using Approach 1 and USEtox 2.1. Ecotoxicological HC50 values are replaced with HC50 values based on geometric means of bacterial MSC distributions acquired from the EUCAST database (accessed 11 Nov 2020)

Antibiotic	ABR enrichment charaterization factor [PAF m^3 day kg^{-1}]
Ampicillin	7.27E + 05
Amoxicillin	1.89E + 06
Cephalexin	5.75E + 05
Ciprofloxacin	5.55E + 04
Colistin	1.63E + 06
Doxycycline	3.49E + 05
Florfenicol	1.27E + 06
Kanamycin	4.43E + 05
Levofloxacin hydrate	2.39E + 07
Rifampicin	1.16E + 08
Sulfamethoxazole	1.00E + 05
Trimethoprim	9.87E + 05
Erythromycin	2.85E + 05
Roxithromycin	3.65E + 05

3.2.2 Approach 2: characterizing human health impacts for ABR (endpoint)

Our alternative approach for establishing linear dose-response relationships between AB use and ABR consequences for human well-being is conceptualized in Fig. 2. Ideally, one would quantify each pathway individually, but data scarcity currently forces us to exercise a generalized mass balance approach where only pathways 1, 2, 4, 6, 9, and 10 are aggregated into one pathway (Fig. 2). Our proposed linear dose-response model assumes that any use of ABs will contribute to resistance development, which allows us to circumvent the shortcomings in data connecting environmental ABR to human health impacts. This implies a loss of ecological relevance, but enables quantification of potential impacts from AB use at regional scales. Data sourced to support the approach are presented in supplementary information (Tables S2, S3, and S4 in supplementary information).

The relationship between AB use and ABR development is inferred by the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report, which presents logistic regression models correlating use of 21 different ABs from five classes in human and food-animal production in the EU and resistance development in five human pathogens (*Salmonella* spp., *Campylobacter coli*, *C. jejuni*, *Escherichia coli*, and *Enterococci*) (European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), and European Medicines Agency (EMA) 2017). This report calculates odds ratios based on logistic regression analysis of AB use data and resistance development data to suggest statistically correlated associations between human and animal consumption of antibiotics, and resistance development in selected human pathogens. Odds ratios are explained by Szumilas (2010, p227) as the representation of "the chance that an outcome will occur given a particular exposure compared to the odds of the outcome occurring in the absence of that exposure".

In LCA, the endpoint of toxicological impact to humans is expressed as disability adjusted life years (DALY), a metric that accounts for the years lost due to premature mortality and productive life due to disability, and is globally scalable (Murray and Lopez 1994). We therefore argue that the common unit for ABR impacts to human health would be the same, given that it is a well-established concept in LCA's cause-effect endpoint pathways. Data available on the impacts to human health have been published by Cassini et al. (2019), who produced an extensive report on the human health impacts from AB-resistant pathogens within the EU health care system, attributing DALYs to 16 pathogen-ABR combinations.

We subsequently use the impact pathway between AB use and DALYs to account for AB use in human and veterinary medicine respectively (1 and 2 in Fig. 2) in the EU, by establishing a causal relationship between AB use and ABR development (4 and 6 in Fig. 2) together with the impacts caused by the subsequent failure to treat infections due to ABR (9 and 10 in Fig. 2). We argue that the use and effect pathways should be parameterized according to the region of interest (country or continental scale), since availability and enforcement of local and regional policy will arguably shape the use and misuse patterns of ABs at each level (Laxminarayan and Malani 2007; Søgaard Jørgensen et al. 2020).

To build a model for expressing DALYs as a product of AB use, we rely on published odds ratio data from the JIACRA report (given that there is a significant correlation (e.g. CI does not cross 1 and $p < 0.05$)) to express a correlation coefficient between the use and resistance development for the investigated AB as

$$\partial_{x,p,sector,reg} = \sqrt{ln^{OR_{x,p,sector,reg}}} \tag{4}$$

where

$\partial_{x,p,\mathrm{sector,reg}}$ = correlation coefficient explaining the relationship between use in the investigated sector (human or veterinary) and resistance development in pathogen p to antibiotic x in the investigated region.

$\mathrm{OR}_{x,\mathrm{sector,reg}}$ = odds ratio implying the strength of association between use of AB x and resistance development for each pathogen p in the investigated sector and region.

Since odds ratio values range between 0 to infinity, we express this coefficient as the square root of ln OR to not suggest an overrepresentation of the odds for resistance development in a particular sector. This correlation coefficient is subsequently used to imply an effect from AB use on resistance development, expressed as

$$ABF_{x,p,reg} = ABU_{x,hum,reg} \times \partial_{x,p,hum,reg} + ABU_{x,vet,reg} \times \partial_{x,p,vet,reg} \tag{5}$$

where

$\mathrm{ABF}_{x,p,\mathrm{reg}}$ = total resistance developed in pathogen p from use of antibiotic x in the investigated region (resistance per kg year^{-1}).

$\mathrm{ABU}_{x,\mathrm{hum,reg}}$ = total use of antibiotic x in human health sector in the investigated region (kg year^{-1}).

$\partial_{x,p,\mathrm{hum,reg}}$ = correlation coefficient explaining relationship between human use and resistance development in pathogen p to antibiotic x in the investigated region.

$\mathrm{ABU}_{x,\mathrm{vet,reg}}$ = total use of antibiotic x in veterinary sector in the investigated region (kg year^{-1}).

$\partial_{x,\mathrm{vet,region}}$ = correlation coefficient explaining relationship between veterinary sector use and resistance development in pathogen p to antibiotic x in the investigated region.

Next, the pathways between ABF to ABR related impacts need to be defined (9 in Fig. 2). This step needs to be aggregated with the subsequent effect; loss of lives, and prolonged hospitalization (10 in Fig. 2), here expressed as

$\mathrm{DALY}_{x,p,\mathrm{reg}}$ = disability adjusted life years attributed to resistance to AB x in pathogen p per region and year.

This gives us a mass balance approach attributing DALYs per kg AB used in the investigated region expressed as

$$\frac{DALY}{kg\ AB_{x_{emitted}}} = \frac{DALY_{x,p_1,reg}}{ABF_{x,p_1,reg}} + \frac{DALY_{x,p_2,reg}}{ABF_{x,p_2,reg}} + \cdots + \frac{DALY_{x,p_n,reg}}{ABF_{x,p_n,reg}} \tag{6}$$

To demonstrate our proposed cause-effect pathway, we allocate DALYs to the use of 3rd-generation cephalosporin (3GC) in EU, a group of beta-lactam antibiotics to which 18 ABs belong. This class of ABs is classified as critically

important for human medicine (World Health Organization 2019), yet is still used within food-animal production to some extent (European Medicines Agency 2019). 3GC resistance is also among the top contributors to pathogen-ABR related mortalities in the EU (Cassini et al. 2019). Following the pathways of Fig. 2, we initially establish quantities of 3GC used in the EU for 2015. According to the ECDC Database (accessed 2020-09-17), close to 270 tonnes of 3GC were used for human treatment (both community and hospital use) in 2015 (Table S2), while the European Medicines Agency (2017) reports 13.9 tonnes 3GC used in animal husbandry that same year, totalling about 284 tonnes annually.

Data are available on odds ratios from the JIACRA report (European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA) 2017) for human consumption of 3rd- and 4th-generation cephalosporin antibiotics (3GC) and resistance development in human pathogen *E. coli.* Note that use of 3rd-generation and 4th-generation cephalosporins is reported as a sum, but will be addressed as 3GC in this example for simplicity. The reported odds ratio for this specific AB-pathogen combination is 1.94 (CI 1.47–2.54, p-value < 0.001), which implies that odds are 94% for resistance to develop in *E. coli* for each increased defined daily dose of 3GC in the human sector. For the veterinary sector, however, the report shows no statistically significant correlation between animal consumption of 3GC and resistance development in the human pathogen *E. coli* (odds ratio 4.13 CI 0.78–21.08, p-value < 0.094), and $\partial_{x,\text{vet,region}}$ will hence be accounted for as "0".

Cassini et al. (2019) report that the most critical pathogen resistance related–infections to human health is 3GC resistant *Escherichia coli*. This pathogen caused a median number of 37.2 DALYs per 100,000 population reported in 2015; 191 883 DALYs across Europe this year given a population of 515.8 million. We input data into our model Eq. 7 according to Eqs. 4, 5, and 6:

$$\frac{DALY}{kg\ AB_{x_{emitted}}} = \frac{DALY_{x,p,reg}}{ABU_{x,hum,\text{reg}} \times \sqrt{ln^{OR_{x,p,\text{hum,reg}}}} + ABU_{x,vet,reg} \times \sqrt{ln^{OR_{x,p,vet,reg}}}} \tag{7}$$

which yields the following for our pathogen-resistance combination *E. coli* infections resistant to 3GC example (Eq. 8):

$$\frac{0.87\ DALY}{kg\ 3GC_{emitted}} = \frac{191883\ DALY}{2.7 \cdot 10^5 kg \times 0,81406 + 1.39 \cdot 10^4 kg \times 0} \tag{8}$$

To put this in perspective, we compare our 0.873 DALYs kg^{-1} AB with the single available characterization of a cephalosporin-class AB, Cefaclor, a 2nd-generation cephalosporin, characterized by Ortiz de García et al. (2017) using USEtox methodology (i.e. non-homologous methodology as to the case above). Ortiz de García et al. (2017) report that the median attributed DALYs are $5.48*10^{-8}$ DALY per $kg_{emitted}$ as non-carcinogenic impact (ranging from $8.62*10^{-12}$ DALY per $kg_{emitted}$ to $1.98*10^{-8}$ DALY per $kg_{emitted}$ depending on emission compartment selected).

This example shows that causal relationships are possible to infer between AB use and DALYs, but overlooks several important aspects and suffers from data scarcity. Nonetheless, we manage to establish a CF_{ABR} for 3GC that associates seven orders of magnitude higher DALYs per kg of AB compared to a CF for a related AB which only considers direct toxicity impacts on humans. It should be noted, that 3GC is the only AB with enough data available to describe this pathway in a European setting currently. For instance, Cassini et al. (2019) do attribute DALYs to another pathogen resistant to 3GC, but there is no available odds ratio for this combination in the JIACRA report (European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA) 2017) and characterizing additional ABs using this linear dose-response concept will require substantial data collection at regional levels. However, as data are continuously being generated and reported, we would expect that the coverage of this approach could be expanded in the future (Limmathurotsakul et al. 2019).

Our endpoint approach is designed to characterize AB use in both human health and veterinary sectors, to account for total use of antibiotics within a region following the One Health concept, acknowledging that ABs can promote ABR regardless of sector. Ideally, refining Eq. 5 to include emissions of ABs at a production stage would improve the model even further, but data on the amounts of ABs emitted during production are largely nonexistent, while they are reported to be substantial in some areas (Larsson 2014; el Balkiny 2014). Despite that this dose-response concept is an oversimplification of the complex cause-effect pathways connecting AB use, resistance development, dissemination, and human health impacts, we still had to aggregate stages in the pathway. Also, considering the limited data availability on ABR-related human impacts, only 16 pathogen-resistance combinations are available from Cassini et al. (2019), which limits the applicability of this approach. ABR frequencies and damage to human health caused by economic and nutritional losses from livestock mortalities are neither considered in our example (11–14 in Fig. 2), though Innes et al. (2019) have proposed a model to account for economic losses in a US setting which could possibly be included at further

development of this model. Additional economic costs from prolonged hospitalizations due to resistant infections is neither included in our model, which is focusing on health impacts, but a similar approach could possibly be included using life cycle costing (Estevan and Schaefer 2017). Moreover, we limit ourselves to a European setting where AB use could be expected to be fairly well regulated, including proper reporting on and administration of drugs, destruction of excess drugs, full treatment cycles of patients and animals, and possible preliminary screenings for ABR genes. The current practical applicability to LCA of this suggested approach could be questioned since there is no ability to compartmentalize emissions and suggest impacts related to various environments. The assumptions made for the linear dose-response concept completely disregard the beneficial aspects of AB use since many lives are saved each year by these pharmaceuticals and modern medicine relies upon functional antibiotics, but the reasoning of human health benefits holds true for the many other chemicals as well, and could be discussed with a broader audience. Conclusively, applying this type of simplified linear dose-response concept for AB use while circumventing stochastic dynamics of ABR development and the contribution of resistance from the environmental compartment will imply statistical inference without causality.

Since there is no available methodology to extrapolate how environmental ABR impacts human health in an LCA context, we had to create two separate pathways, one prospective method which looks at the onset of ABR in environmental bacteria using the established characterization model USEtox, and a second retrospective method based on statistical correlations between AB use and human health impacts. Since these models are based on different assumptions with little commonality, they express different strengths and shortcomings that need to be considered before implementation. We view these two novel AB characterization methodologies as steppingstones to further refinements and discussions on the holistic assessment of ABs and resistance development in LCA.

4 Conclusions

ABs have been assumed to contribute to ecotoxicity and human toxicity in seventeen LCAs, but the latter impact category is sparsely characterized. Moreover, ABR impacts as a consequence of AB use have not yet been accounted for in LCA, which suggests that the full impacts of AB use in LCAs are severely underestimated. In response, we present two approaches that acknowledge these impacts and that can be readily included in existing impact assessment models to generate characterization factors for ABR enrichment in the environment at a mid-point level, and a correlation between AB use and DALYs for endpoint impacts. The mid-point characterization approach for ABR enrichment in the environment provides a robust comparative model for assessing AB use or removal from wastewater, agriculture, or industrial processes. Further development of this methodology would benefit from refining the current MIC to MSC extrapolations since a fair amount of AB MIC data are available. For the endpoint approach, we use 3GC as an example to prove the concept of our theory, but few causal relationships and data limitations challenge the practical usefulness of this approach at present. We would therefore recommend caution when interpreting human health impacts from ABs in LCA studies until more holistic methodologies and better data become available. Future LCAs including ABs should ideally adopt a One Health approach and could benefit from complementary environmental risk assessments, allowing for the dynamics of AB use and emission in all relevant sectors to be accounted for.

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