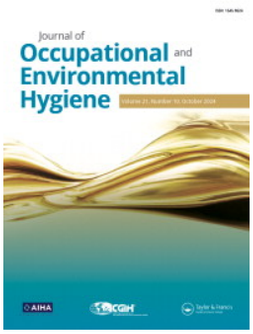

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Preliminary human health risk assessment of antibiotic exposures in human waste handling occupations

Mamadou Niang[a], Tiina Reponen[a], Glenn Talaska[a], Jun Ying[a], John F. Reichard[a], Alison Pecquet[a], and Andrew Maier[b]

[a]Department of Environmental and Public Health Sciences, College of Medicine, University of Cincinnati, Cincinnati, Ohio; [b]Stantec ChemRisk, Cincinnati, Ohio

ABSTRACT

Exposure to biosolids in human waste handling occupations is associated with a risk for illness due to microbial infections. Although several years of exposure to biosolids might be hypothesized to be a prophylaxis against infection, the risks associated with infections from antibiotic-resistant organisms can also be a potential concern. Therefore, this study aimed to conduct a screening level risk assessment by deriving occupational exposure limits (OELs) characterizing the risks of adverse health effects among workers in human waste handling occupations with a focus on exposure to two pharmaceuticals commonly found in biosolids: ciprofloxacin (CIP) and azithromycin (AZ). Epidemiological and exposure studies of workers exposed to biosolids were identified through searches of major scientific databases. Screening OELs (sOELs) for these antibiotics were derived using a standardized methodology. The airborne concentrations of CIP and AZ antibiotics were determined using an exposure factors approach. The health-based exposure limits (i.e., sOELs) and the acceptable daily exposure (ADE) values for both of these antibiotics were derived as 80 μg/m^3 and 12 μg/kg-day, respectively. An exposure factor approach suggested that inhalation route exposures to CIP and AZ are well below the sOELs and ADE daily doses, and likely too low to cause direct adverse health effects through antibiotic inhalation. A critical review of epidemiological studies on different occupations handling biosolids showed that the workers in industries with potential biosolids exposure have experienced an increased incidence of microbial-exposure-related illness. The health effects seen in the workers have been attributed to bacterial, viral, and protozoan infections. To the extent that bacteria are the pathogen of concern, it is not clear whether these bacteria are resistant to antibiotics commonly found in biosolids. It is also unclear whether the presence of antibiotics or antibiotic-resistant bacteria increases the susceptibility of these workers. Additional studies will provide more definitive estimates of inhalation and dermal exposures to CIP and AZ and could verify the exposure estimates in this study based on the literature and common exposure factors.

KEYWORDS

Allowable daily exposure; azithromycin; biosolids; ciprofloxacin; occupational exposure limit; sampling

Introduction

The term biosolids refers to the residues (treated sewage sludge) generated after the treatment processes of domestic, municipal, and industrial wastewater. These residues, which come in solid, semi-solid, or liquid form, are a mixture of inorganic contaminants (e.g., metals and trace elements), organic contaminants (e.g., polychlorinated biphenyls, dioxins, pharmaceuticals, and surfactants), and pathogens (e.g., fungi, protozoa, bacteria, viruses, and parasites) (NRC 2002). Sludge treatment processes are intended to remove a significant portion of organic and inorganic contaminants as well as disease-causing organisms so that the United States Environmental Protection Agency (EPA) pollutant and pathogen requirements for land application and surface disposal are met (NRC 2002).

Globally, the general guidelines for sludge recovery, recycling, treatment, and the land application of biosolids and biosolids-derived products for other beneficial uses (e.g., land reclamation or rehabilitation) are contained in the International Organization for Standardization (ISO) 19698:2020 Sludge Recovery, Recycling, Treatment, and Disposal – Beneficial Use of Biosolids – Land Application (ISO 2020). In the United States, the federal biosolids regulations on use and disposal practices, pollutant limits, management practices, and operational standards are contained in the 40 CFR Part 503 Standards for the Use or

CONTACT Mamadou Niang m.niang69@yahoo.com Department of Environmental and Public Health Sciences, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Disposal of Sewage Sludge (USEPA 1994). Class A biosolids have undergone treatment processes to reduce the concentrations of pathogens below detectable levels; therefore, no federal restrictions are needed when used for land application. In contrast, Class B biosolids have undergone treatment processes to reduce pathogen concentrations to a very low level that is protective of public health and the environment under specific use conditions (NRC 2002).

Biosolids are mainly used as fertilizers to improve and maintain productive soils and stimulate plant growth (USEPA 1999). Their use includes various types of land applications in agriculture and forestry operations, land rehabilitation, landscaping and topsoil, composting, and use in incinerators. Other uses of biosolids include rehabilitating mining sites, brick and construction material production, vitrification (glass manufacture), and use as biofuels, fuel substitutes in cement plants, and as a road base (USEPA 1999; Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health 2002).

Many occupations involve handling human waste streams, including biosolids users (farmers and landscapers), workers involved in biosolids production and application (wastewater treatment workers and aseptic tank company workers), and compost workers. Agriculture workers such as farmers started to use sludge from wastewater treatment plants as fertilizer as early as the 1920s after the scientific and agricultural communities found that biosolids contain valuable nutrients that can improve soil fertility (Gaskin et al. 2012). The liquid form of biosolids can be transported by truck to a land application site where it is applied directly to the soil (Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health 2002). Therefore, workers involved in the transport and land application of liquid biosolids as well as aseptic tank workers who use vacuum trucks to clean septic tanks can be exposed to biosolids.

Workers exposed to Class B biosolids may be at greater risk of developing diseases due to the presence of viable pathogens in biosolids (NRC 2002). While the EPA restricts public access to land where Class B biosolids are applied, this restriction does not apply to workers involved in the land application (Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health 2002). A worker's risk of developing diseases depends on the (1) number and type of pathogens present in the Class B biosolid, (2) infective and received dose of the pathogens, (3) route of exposure, and (4) susceptibility of the exposed worker (Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health 2002). Although it was suggested that exposure to wastewater could protect workers against these microorganisms by providing immunologic prophylaxis (LeChevallier et al. 2020), epidemiological studies have shown that workers in these industries have an increased incidence of illness, ranging from acute to chronic diseases, and cancers (Burton and Trout 1999; Gregersen et al. 1999; Schlosser et al. 1999; Trout et al. 2000; Weldon et al. 2000; Alvarado-Esquivel et al. 2010). For example, a NIOSH field investigation uncovered repeated instances of gastrointestinal illness reported by workers after exposure to biosolids (Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health 2002). More recently, concerns about wastewater worker safety during the current COVID-19 pandemic have been growing since various authors have warned that the application of sludge and biosolids carries a significant risk for illness due to exposure to the SARS-CoV-2 virus and the development of COVID-19 (Patel et al. 2020; Langone et al. 2021). The concern for the development of COVID-19 is particularly relevant as this suggests the potential for inhalation exposures.

Workers can be exposed to human waste streams such as raw sewage, class A, and class B biosolids with the predominant form depending on the occupation. Workplace exposure to biosolids occurs primarily through three routes: inhalation, ingestion, and dermal contact. Chemicals in biosolids have the potential to become airborne and move into a worker's breathing zone. Ingestion exposure can occur by touching the face with contaminated hands or gloves or during eating, drinking, or smoking in the absence of effective hand hygiene. Gastrointestinal tract exposures can arise from the swallowing of inhaled materials. Dermal exposure occurs when workers handle biosolids directly in the absence of appropriate chemical protective clothing. In addition, chemicals contained in airborne biosolid particles can be deposited directly onto worker's skin, or biosolids can be deposited onto their clothing or work surfaces and transferred to the skin when the clothing or surface is touched.

Along with human biosolid waste, wastewater treatment workers are exposed to chemical substances, including pharmaceuticals, drugs, and drug metabolites from domestic, commercial, or industrial waste. Wastewater Treatment Plants (WWTPs) and municipal solid waste (MSW) operations generate approximately 8 and 77 million dry tons of biosolids, respectively, each year in the United States, and the biosolids contain relatively high concentrations of active pharmaceutical ingredients (APIs) commonly

found in a variety of household products and drugs (USEPA 2015). Following dose administration, many APIs are excreted either unaltered in their parent form or as metabolites. Most antibiotics are only partially metabolized by humans after administration, suggesting the release of active antibiotics in their original form into waste streams. For example, up to 60% of ciprofloxacin (CIP) and 75% of azithromycin (AZ) are excreted from the human body as unaltered parent compounds and can accumulate in sewage sludge (Girardi et al. 2011). Therefore, significant amounts of prescribed antibiotics and their metabolites are excreted and present in domestic, municipal, or industrial wastewater. The technology that is commonly used in conventional WWTPs is not specifically designed to remove pharmaceuticals from sludges (Silva et al. 2019). Consequently, a large portion of pharmaceuticals can survive the treatment process and accumulate in sewage sludge and biosolids (treated sewage sludge). Therefore, it is critical to derive health-based exposure limits for contaminants found in biosolids and to monitor worker exposure to conduct informed occupational risk assessments.

In pharmaceutical manufacturing, health-based exposure limits for product quality assessment are called permissible daily exposures (PDE) or acceptable daily exposures (ADE) (Sargent et al. 2013, 2016). ADEs represent an estimate of the maximum daily dose of an API that is not expected to result in adverse noncancer effects by any route over a lifetime (Sargent et al. 2013). For workers, the relevant health-based exposure limit is an occupational exposure limit (OEL). OELs provide a benchmark for characterizing the risk of occupational exposure to pharmaceuticals and other chemicals. The process for the setting of an OEL or ADE is similar and involves a robust evaluation of toxicology data to identify the critical effect (the most sensitive adverse effect) and the point of departure (PoD – the estimated onset dose boundary for the critical effect) (Bercu et al. 2016). The PoD is then adjusted for additional considerations, such as duration and route of exposure to estimate an adjusted PoD (Reichard et al. 2016). Further refinement of the PoD dose is made through the application of assessment factors that account for sources of biological response variability and limitations in extrapolations from the clinical and non-clinical health effects data (Bercu et al. 2016; Sargent et al. 2016; Sussman et al. 2016). The final product of this derivation procedure is an air concentration to which it is anticipated that a worker could be exposed without the onset of adverse health effects. There are currently no OELs published from authoritative organizations for CIP or AZ; however, drug manufacturers have derived internal OELs and published them on their safety data sheets (SDSs). For example, the OEL as an 8-h time-weighted average (TWA) is 600 $\mu g/m^3$ for CIP and 500 $\mu g/m^3$ for AZ (Pfizer 2015, 2018). These two antibiotics are also on the list of chemicals being evaluated by the Workplace Environmental Exposure Level (WEEL) Committee (OARS WEEL 2023), suggesting the future availability of a more definitive expert group-based OEL. In the absence of any published OELs from public agencies, provisional OELs (pOELs) were derived to support a screening-level risk assessment. This risk assessment aimed to estimate airborne concentrations of these pharmaceuticals based on available exposure factors and characterize the potential for health hazards in human waste occupations

Methods

Derivation of health-protective OEL/ADE for ciprofloxacin and azithromycin

Identification of the critical effect and PoD was based on data found in clinical and nonclinical studies. In the hazard assessment, the available toxicology literature was evaluated by searching general databases at the University of Cincinnati Library.

Sufficient data was available to derive pOELs for both antibiotics. These health-based limits are presented in two forms. First, an ADE was derived based on allowable mass exposure/day using principles to those described in the International Council on Harmonization (ICH) guidelines (ICH Q3C 2022). Next, the screening OEL (sOEL) was calculated using the same inputs as the ADE but also accounted for inhalation bioavailability of the drug, worker's body weight, and air intake rate. The ADE and sOEL for these specified antibiotics were derived using the therapeutic dose or critical adverse effect from the toxicology literature as a PoD and adjustment factors to account for various uncertainties when extrapolating from the PoD. The ADE (Equation 1) and sOEL (Equation 2) derivation followed methodology and considerations described based on Bercu et al. (2016) guidelines for the PoD selection and Sussman et al. (2016) recommendation for the application of adjustment factors (AFs) for pharmaceutical risk assessment.

$$\mathrm{ADE}\left(\mathrm{mg/kg\text{-}day}\right) = \frac{\mathrm{PoD}\left(\frac{\mathrm{mg}}{\mathrm{kg}}/\mathrm{day}\right)}{\mathrm{Composite\ AF}} \qquad (1)$$

where:

Composite AF = reflects the product of factors F_1 through F_5.

F_1 = AF for animal-to-human extrapolation

F_2 = AF for human variability

F_3 = AF for shorter- to longer-term exposure duration extrapolation

F_4 = AF for database completeness, to address the potential for additional sensitive or severe effects.

F_5 = AF for extrapolation from the lowest-observed-adverse-effect level (LOAEL) to no-observed-adverse-effect level (NOAEL)

Any studies that were applicable for use in risk assessment were evaluated for the most sensitive relevant adverse effect to determine the PoD. Once PoD values were identified and adjusted for occupationally relevant dose durations, composite AFs were applied. The composite AF reflects the product of factors F_1 through F_5. The data used as the basis for dose response were primarily via the oral route. The consideration or route bioavailability was included as a bioavailability adjustment factor (BAF) in the composite AF. The BAF is the ratio of the bioavailability for the route of interest (inhalation in this assessment) and the bioavailability for the route for which the PoD study was identified (oral dosing for this assessment). Since these antibiotics are small molecules with relatively high (but varying reported levels of oral bioavailability), it was assumed that the oral and inhalation bioavailability are similar, and thus a BAF value of 1 was used. Uncertainty related to this approach was considered to be addressed in the application of the AF related to database limitations (F_4).

The sOEL for inhalation exposure was calculated using Equation 2 by assuming the body weight (BW) of 70 kg for a worker and a protective default 8-h inhalation air volume of 10 cubic meters. For both antibiotics, the assumed inhaled dose deposition and bioavailability was 100%, and thus, the specific inclusion of this consideration in the equation is not shown.

$$\mathrm{sOEL}\left(\mathrm{mg/m^3}\right) = \frac{PoD\left(\frac{mg}{Kg}/day\right) * BW(Kg)}{AF * Volume\ of\ air\left(\frac{\mathrm{m3}}{day}\right)} \qquad (2)$$

where:

AF = reflects the product of factors F_1 through F_5 as described for the ADE equation

Literature review

General databases at the University of Cincinnati (https://www.libraries.uc.edu/), which use search engines such as Web of Science, Scopus (Elsevier), PubMed, Academic Search Complete, Summon, and ProQuest were used to search articles. The following keywords were used to identify relevant epidemiological and biosolid aerosol exposure studies: "ciprofloxacin," "azithromycin," "land application," "biosolids," "concentration," "amount," "air," "antimicrobial," "antibiotics," "pharmaceutical," "workers," "occupations," "setting," "plumbers," "farmers," "sewages," "wastewater treatment," "setting," "aseptic tank," "composting," "agriculture," "air sampling," "exposure," "epidemiology," "disease," "illness," "symptoms," "health," "effect," "impact," "immune," "modulators," "immunotoxicity," "immune system," "trigger," "blood," "urine," "sample," "particulate matter," "total," "compounds," "chemicals," "bioaerosols," "bio sampling," "biological sampling," "microorganism," and "pathogens." Since the number of articles in epidemiological, bulk sampling, and particulate matter studies is relatively limited, no restriction was made for the date of publication. In total, 5,442 potential records were identified through searching the University of Cincinnati databases. This included 116 epidemiological studies, 48 bulk sampling studies, 1,246 microbiological sampling studies, and 3,921 particulate matter studies (Figure 1). After reading the titles and the abstracts, 5,266 of the retrieved articles were immediately rejected because they were not relevant to the aim of this study. Out of 176 relevant articles screened, 131 were excluded because they were systematic reviews or meta-analyses, animal studies, or duplicates. Finally, the remaining 45 articles assessed for eligibility were included in this paper.

To address the question of the amount of airborne CIP and AZ found at human waste handling sites, it is important to consider the types of information available. A preliminary literature review showed no studies on measured airborne concentrations of the two antibiotics in biosolids handling occupations. However, concentrations of these chemicals were measured in biosolids materials. Knowing that these two antibiotics in biosolids materials are not volatile and having the concentration of these chemicals in biosolids materials, another literature review was conducted focusing on studies that included measurements of total particulate exposures in these occupations. This would allow for an estimation of the concentration of antibiotics in airborne biosolids particulates, and therefore an estimate for occupational exposure. The 8-hr TWA concentration of total particles found in the Epstein et al. (2001) study was used as an estimate of the total concentration of biosolid aerosol concentrations for various waste-handling operations. Furthermore, it was conservatively assumed that the overall bioavailability of airborne

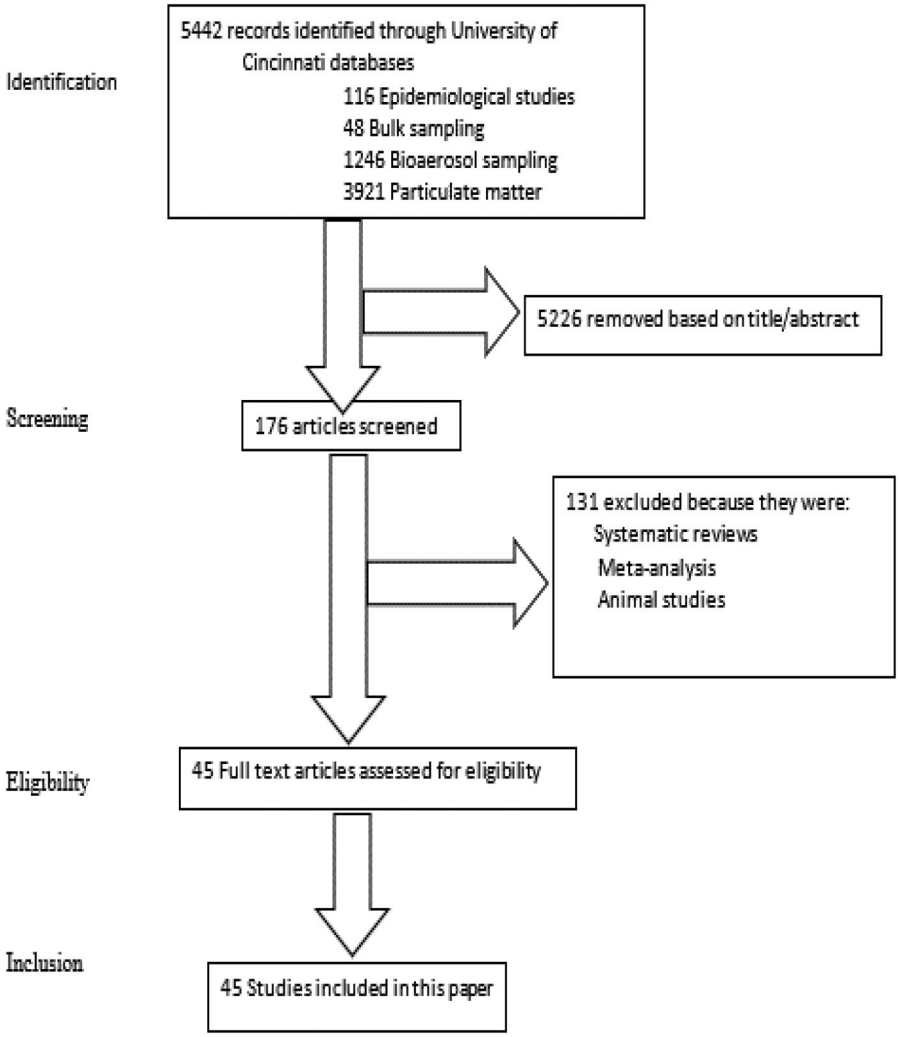

Figure 1. Flow chart for selection of studies in the literature review.

particles inhaled was 100% (i.e., that all the measured aerosol was inhalable, deposited in the respiratory tract, and available for systemic uptake) (Reichard et al. 2016). The airborne concentrations of CIP and AZ antibiotics were determined using Equation 3:

$$C = Cm * Cp \quad (3)$$

where:

C = Concentration of airborne ciprofloxacin or azithromycin ($\mu g/m^3$)

C_m = Concentration (mass %) of ciprofloxacin or azithromycin (μg/per kilogram (i.e.,10^9 μg) of biosolids)

C_p = Concentration of airborne biosolid aerosol found in the Epstein et al. study (1410 $\mu g/m^3$) (Epstein et al. 2001).

For risk characterization, a hazard quotient (HQ) was used. HQ is defined as the ratio of exposure to an appropriate health-based limit, such as the OEL (Goumenou and Tsatsakis 2019). It is a method used to compare exposure data to the health-based limit and calculated using Equation 4 (Waters et al. 2015). The HQ is generally interpreted as such that as the HQ approaches and exceeds a value of 1, this is an indication of a potential increased risk of adverse effects. Values far below 1 suggest little concern, whereas values well above 1 are viewed as increasingly of concern.

$$HQ = \frac{EE}{OEL} \quad (4)$$

where:

HQ = Hazard quotient

EE = Exposure estimate ($\mu g/m^3$)

OEL = Occupational exposure limit ($\mu g/m^3$)

Because the Epstein et al. (2001) study used 8-h TWA, the calculated CIP and AZ antibiotics concentrations were directly used as the EEs.

Results

For both antibiotics, all available clinical and nonclinical toxicology data were assessed to identify the PoD

for use in deriving the pOELs. The potential key health endpoints and PoD options are summarized below. A summary of the available key data found in the literature survey for each antibiotic is summarized in Section 3.

Ciprofloxacin

Available health-based exposure limits

For CIP, no OELs were identified in the published literature or from organizations that publish health-based OELs. An 8-h TWA OEL recommendation of 600 μg/m^3 was identified from a manufacturer's SDS (Pfizer 2018). The WEEL Committee currently has listed this antibiotic as under study for OEL development, but a value has not been published (OARS WEEL 2023). Other health-based exposure limits have been published for systemic exposures. Schwab et al. (2005) derived an acceptable daily intake (ADI) of 1.6 μg/kg/day based on the bacterial minimum inhibitory concentration as a PoD with no additional adjustment factors applied. The ADI refers to the amount of a compound that can be consumed daily over a lifetime without producing an adverse effect (Renwick 1991). Multiplying this ADI by an assumed body weight of 70 kg for a worker and dividing it by a work-day inhalation volume of 10 m^3 resulted in an OEL equivalent of 11 μg/m^3. McAvoy et al. (2019) developed a reference dose value (RfD) for application to biosolids risk assessments for the general population. The minimum therapeutic dose was used as a PoD based on the presence of adverse side effects (gastrointestinal system, central nervous system, liver, and phototoxicity for CIP and cardiotoxicity for AZ), and a composite adjustment factor of 1000 was applied to yield an RfD of 4 μg/kg-day. Adjusting for worker body weight and breathing rate resulted in an OEL equivalent of 28 μg/m^3. Note that these conversions of general population daily limits may be more than adequately protective for workers as they assume greater individual susceptibility for the general population than may occur in a generally healthy workforce (Dankovic et al. 2015).

Clinical Pharmacokinetic Information

Data on CIP clinical pharmacokinetics were identified for inhalation exposure. Stass et al. (2013) investigated the safety and tolerability of CIP dry powder for inhalation (DPI) in healthy male subjects and found that CIP DPI was well tolerated with no clinically relevant adverse effects on lung function. Pharmacokinetic modeling and clearance data suggest that approximately 40% of the total dose of CIP DPI reached the tracheobronchial region and alveolar space and the clearance of CIP from the tracheobronchial region was slower compared with that from the alveolar space (Stass et al. 2013). Based on the low molecular weight (MW = 367 g/mol), CIP likely has high inhalation bioavailability (Gandomkarzadeh et al. 2020). Concerning bioavailability following an oral administration of single doses of 250, 500, and 750 mg tablets of ciprofloxacin, the absolute bioavailability is approximately 70–80% with no substantial loss by first-pass metabolism (Medsafe 2012). CIP is widely distributed to tissues based on its volume of distribution. CIP is cleared from the combination of hepatic metabolism with urinary excretion. Two clinical studies using intravenous and oral dosing demonstrated that systematic clearance is relatively rapid, with serum half-life values ranging from 3.13 to 4.0 hr (Gonzalez et al. 1985). This suggests little potential for cross-shift dose accumulation in exposed workers.

Clinical and nonclinical toxicology

Clinical and nonclinical toxicology articles were summarized to provide a general overview of CIP *in vivo* toxicity in humans and animals. Clinical toxicology focused on the toxic effects caused by CIP on humans, while non clinical toxicology involved the potential adverse effects caused by this antibiotic in animals.

Cardiotoxicity: Clinical toxicology. Several authors have studied the ability of CIP to modulate cardiac rhythm with mixed results. In a prospective study of 38 patients who received CIP, Makaryus et al. (2006) reported no significant prolonged QTc interval over baseline. In contrast, Adikwu and Brambaifa (2012) and Prabhakar and Krahn (2004) have shown an association between QT prolongation and arrhythmia in patients following CIP administration. This is a very important adverse effect that has led to the market withdrawal of several fluoroquinolones.

Cardiotoxicity: Nonclinical toxicology. Myocardiotoxicity was evaluated in healthy juvenile rats administered 0, 25, or 50 mg/kg CIP twice a day for one week (Al-faris et al. 2011). Increased serum levels of lactate dehydrogenase (LDH) levels were increased in the low-dose group, and additional serum markers of cardiotoxicity were increased at the high dose. Histopathological cardiac changes were observed in both treatment groups. This study identifies a LOAEL of 50 mg/kg-day for cardiotoxicity.

Arthropathy: Clinical toxicology. CIP is contraindicated in children, growing adolescents, and during pregnancy due to the potential for toxicity targeting the joints. Patients in clinical trials taking 250 mg/kg twice daily orally have an increased incidence of arthropathy relative to the control group. Reported signs and symptoms included an increased risk of tendinitis and tendon rupture, but the occurrence is rare (Zhang et al. 2017). The potential for joint-related pathology has been investigated using mechanistic studies. Decreased cell proliferation of human chondrocytes in cell culture was demonstrated by Mont et al. (1996) at doses that are equal to or greater than therapeutic serum levels. Other authors such as Menschik et al. (1997) observed chondrocyte toxicity and necrosis following the incubation of human adult cartilage biopsy specimens with a 1 and 10 mg dose of ciprofloxacin for two weeks.

Arthropathy: Nonclinical toxicology. CIP generates pathology in the joints. This effect has been studied in juvenile dogs in several studies that employed repeated doses with acute or subacute study designs with oral dosing (US NIH 2011). Among these studies, a NOAEL of 10 mg/kg-day was observed in a two-week dosing regimen with adverse joint lesions observed at 30 mg/kg-day. The effects of CIP are attributed to antagonistic effects of magnesium (Shakibaei et al. 2001). A study in mice to test the impacts of CIP during post-natal development reported increased inflammation of the knee joint at a dose of 100 mg/kg-day, but not at 30 mg/kg-day when administered on post-natal days 2 to 12 via subcutaneous injection (Bourgeois et al. 2016).

Reproductive and developmental toxicity: Clinical toxicology. Some postmarketing surveillance studies of limited sample size have been conducted for patients taking CIP. In general, these studies did not identify drug-related differences from controls in pregnancy-related outcomes. A review by an expert group (the Teratogen Information System) concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk. Their review also noted that data are insufficient to state that there is no risk (FDA 2002).

Reproductive/developmental toxicity: Nonclinical toxicology. Schluter (1989) studied CIP in cynomolgus monkeys given 0 or 200 mg/kg from days 20–50 of pregnancy. No increase in abortions and no differences between the progesterone levels of controls or exposed animals were observed. No effects on embryos or fetal development were reported. This study was corroborated by Christ and Lehnert (1990), who observed no evidence of harm to the fetus following an intravenous administration of ciprofloxacin in rabbits at 20 mg/kg-day. Fertility studies in rats at oral doses as high as 100 mg/kg-day had no effects on fertility (US NIH 2011). The effects on male fertility were evaluated in rats. Khaki et al. (2008) reported decreased sperm concentration, motility, and viability as well as decreased spermatogenic cells in rats given a daily oral dose of 12.5 mg/kg-day for 60 days. Nashwa et al. (2011) similarly reported a 12.5 mg/kg-day dose for 65 days decreased reproductive organ weights, sperm parameters, and altered levels of reproductive hormones and tissue histopathology. Together these studies do not suggest that CIP is a developmental toxicant, except for the noted effects on the nervous system, joints, and liver described for target organ toxicity that coincide with the maternal effect level ranges. However, based on studies in rats, a LOAEL of 12.5 mg/kg-day was identified for male reproductive effects.

Phototoxicity: Clinical toxicology. Vousden et al. (1999) observed mild phototoxicity in 40 healthy male and female volunteers following a repeated dose of 500 mg of CIP for 7 days by evaluation of skin reactions 0–30 min afterward for immediate erythema and 24 and 48 h for delayed erythema.

Acute toxicity, irritancy, and sensitization: Clinical toxicology. No clinical toxicology research was identified to assess potential acute toxicity, irritancy, and sensitization in humans.

Acute toxicity, irritancy, and sensitization: Nonclinical toxicology. No data were identified for acute toxicity or sensitization potential. However, CIP was determined to be an ocular irritant (ECHA 2017).

Nephrotoxicity: Nonclinical toxicology. CIP-induced renal toxicity at moderate doses in rats. Repeated doses of 50 mg/kg-day for one week (Al-Shawi 2012) or 40 mg/kg-day for 10 days (Elbe et al. 2016) induced histopathology changes in the kidney (Al-Shawi 2012; Elbe et al. 2016). An acute dosing study in rhesus monkeys reported crystalluria without nephropathy following single oral doses as low as 5 mg/kg (US NIH 2011). These results support a LOAEL of 40 mg/kg-day, although the relevance of the mode of action to humans is uncertain.

Hepatoxicity: Nonclinical toxicology. The hepatoxicity potential of CIP has been demonstrated in *in vivo* animal studies. Al-Shawi (2012) evaluated the toxicity of CIP on the histology of the liver and kidneys of juvenile rats. Histological examination of the liver demonstrated degeneration and necrosis of the liver at both tested doses of 25 mg/kg and 50 mg/kg twice daily compared to the controls. Channa and Janjua (2003) showed that CIP administered intraperitoneally to pregnant Wistar albino rats at a double therapeutic dose of 20 mg/kg body weight produced a significant degenerative change in the fetal liver. These observed changes in the maternal and fetal livers were supported by Nadia (2006), who administrated oral doses of CIP at therapeutic and double therapeutic doses of 57 and 114 mg/kg at day 1 or day 6 up to day 19 of gestation. All these reports suggested that CIP may have hepatotoxic potential. The data suggests a minimal LOAEL value of 20 mg/kg-day for fetal liver effects.

Neurotoxicity: Nonclinical toxicology. A neurobehavioral study was conducted in rats exposed to single oral daily doses of 20 mg/kg and 50 mg/kg for 14 days (Ilgin et al. 2015). Changes in several metrics of behavior, as well as CNS neurotransmitter levels, were observed at the high dose only. This study identified NOAEL for neurological effects of 20 mg/kg-day. Post-natal subcutaneous injection of 100 mg/kg-day, but not 30 mg/kg-day on post-natal days two to 12 in mice caused impaired psychomotor development (Ilgin et al. 2015).

Genotoxicity and carcinogenicity: Nonclinical toxicology. The carcinogenicity of CIP has been tested in chronic bioassays in mice and rats. Daily administration of CIP at oral dose levels up to 300 or 500 mg/kg in rats for 24 months and 450 mg/kg in mice for up to 21 months, did not find any indication of carcinogenic or tumorigenic effects (Christ and Lehnert 1990). CIP has been extensively tested in many genotoxicity assays (US NIH 2011). The weight of evidence based on mixed results from *in vitro* studies and negative results in *in vivo* studies indicate that CIP is not genotoxic and supports the finding of a lack of tumors in animals.

Clinical health effects summary

CIP is a commonly prescribed antibiotic that is used in treating adults infected with Gram-negative bacteria. Typical dosing regimens range from 250 to 500 mg/day. The fluoroquinolone antibiotics such as CIP are generally well tolerated under typical clinical use. There are several adverse effect notifications and common adverse side effects that cause phototoxicity and impact the gastrointestinal system, central nervous system, and liver. CIP is well tolerated by humans with a relatively low occurrence of adverse side effects (Adikwu and Brambaifa 2012). However, a review of the case studies of patients treated therapeutically with doses of CIP has suggested hepatotoxicity characterized by increased levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, and leukocytes (Adikwu and Brambaifa 2012). A case of hepatic failure with elevated serum transaminases, alkaline phosphatase, gamma-glutamyl transferase, reduced prothrombin time, and elevated serum bilirubin was reported by Zimpfer et al. (2004) in a patient treated with 250 mg ciprofloxacin twice per day. The liver biopsy revealed extensive hepatocellular necrosis involving zones 2 and 3 of the hepatic acini and a mixed inflammatory infiltration containing abundant eosinophils (Zimpfer et al. 2004). Similar findings of induced cholestatic liver injury and acute tubular necrosis were reported by Dichiara et al. (2008) in patients treated with doses of 500 mg twice daily. Hajji et al. (2018) reported acute renal failure in a patient treated with a therapeutic dose as low as 200–250 mg twice daily. Some of the more pertinent clinical findings are summarized below.

Nonclinical clinical health effect summary

CIP induces numerous target organ effects in *in vivo* toxicology studies at a dose that approximates the equivalent minimum therapeutic dose of 3.6 mg/kg-day (250 mg/day/70 kg body weight). Potential effects of interest for OEL derivation include effects on joint health, the kidneys, liver, nervous system, heart, and male reproductive organs. The effects that appear to occur at the lowest doses include arthropathy with a NOAEL of 10 mg/kg-day in a 2-week dosing study in dogs and male reproductive effects in male rats observed with a LOAEL of 12.5 mg/kg-day.

Azithromycin

Available health-based exposure limits

For AZ, there were no available OEL from authoritative agencies or in the published literature. An 8-h TWA OEL recommendation of 500 $\mu g/m^3$ was identified from a manufacturer's SDS (Pfizer 2018). The Workplace Environmental Exposure Level (WEEL) Committee currently has listed this antibiotic as under

study for OEL development, but a value has not been published (OARS WEEL 2023). McAvoy et al. (2019) developed a reference dose value (RfD) for application to biosolids risk assessments. The NOAEL dose of 20 mg/kg-day from a rat study (minimal liver effects were observed at the next highest dose) and a composite adjustment factor of 300 resulted in an RfD of 0.067 mg/kg-day (70 μg/kg-day) (McAvoy et al. 2019). Adjusting for worker body weight and breathing rate resulted in an OEL equivalent of 490 μg/m^3 (rounded to 500 μg/m^3).

Clinical Pharmacokinetic Information

No data on AZ clinical pharmacokinetics were identified for inhalation. However, it is well absorbed orally (Pfizer 2013). A single administration of 500 mg oral and intravenous doses demonstrated a decline in a poly-phasic pattern with a mean apparent plasma clearance of 630 mL/min and a terminal elimination half-life of 68 h (Pfizer 2013). The absolute oral bioavailability of 250 mg capsules is 38% (Riva Laboratoire Inc 2016). An oral administration of AZ demonstrated that it is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg and higher concentrations in tissues compared to plasma or serum (Riva Laboratoire Inc 2016). AZ is mainly cleared from biliary excretion and predominantly as unchanged drug (Pfizer 2013). Nearly 6% of the administered dose appears as an unchanged drug in urine over a week (Pfizer 2013). Due to the absence of AZ clinical pharmacokinetics data for inhalation, it is assumed that AZ has high inhalation bioavailability, and a default inhalation bioavailability factor of 100% is typical for setting inhalation limits for such molecules (Reichard et al. 2016).

Clinical and nonclinical toxicology

Only one clinical toxicology research area was identified to assess the potential toxicity of AZ in humans. Most information on the potential toxicity of AZ comes from nonclinical toxicology.

Cardiotoxicity: Clinical toxicology. Several authors have studied the effect of AZ on cardiac rhythm with consistent findings. In a cohort study of 347,795 patients aged from 30 to 74 years old with no life-threatening non-cardiovascular illnesses, Ray et al. (2012) showed an increased risk of cardiovascular deaths following the prescription of AZ. Svanström et al. (2013) reported an increased risk of death from cardiovascular effects in a large population of young-to-middle-aged adults following AZ treatment in comparison with no use of antibiotics. Prolongation of QT interval and cases of torsade de pointes have been reported in patients following AZ administration (Pfizer 2013).

Cardiotoxicity: Nonclinical toxicology. Arrhythmia mechanisms were evaluated *in vivo* and *in vitro* in guinea pigs' assays. AZ was administered *in vivo* at three times the clinically relevant dose (114.6 mg/kg) and *in vitro* at five to 10 times the clinically relevant dose (207.5 and 415 mg/L) (Zhang et al. 2017). Reduced heart rate and prolonged PR, QRS, and rate-corrected QT (QTc) intervals were reported in the isolated guinea pig heart electrocardiogram (ECG) (Zhang et al. 2017). This study identified a LOAEL of 114.6 mg/kg-day for cardiotoxicity.

Acute toxicity: Nonclinical toxicology. Mayne et al. (1996) studied acute single dosing in albino mice and Sprague-Dawley rats following an oral and intraperitoneal administration of AZ. For an oral dose of AZ greater than or equal to 1,000 mg/kg, soft feces were reported in mice within 1–2 h after dosing (Mayne et al. 1996). When the oral dose of AZ was greater than 1,000 mg/kg, the death of male mice was reported, and the death of female mice was observed at 5,000 mg/kg oral dosage (Mayne et al. 1996). Before the deaths, a short episode of convulsion was observed within several hours of dosing. With an intraperitoneal administration of AZ at a dose greater than or equal to 400 mg/kg, death was observed within several hours after dosing (Mayne et al. 1996). Similar symptoms such as loose stools and decreased activity were observed in rats following an oral administration of 2,000 mg/kg of AZ (Mayne et al. 1996). No death was reported in rats at the same dose. However, deaths were observed in rats following an intraperitoneal administration of AZ at doses greater than or equal to 900 mg/kg (Mayne et al. 1996). Together these data suggest low acute toxicity potential according to current hazard classification systems. Concerning repeated dose systemic toxicity, studies in rats and Beagle dogs have been identified. Liver effects were reported in an oral dosing study in rats with a NOAEL identified as greater than 20 mg/kg for daily dosing (the highest dose tested), although some minimal effects were observed with intermittent dosing to 40 mg/kg (Lundeen et al. 1996). In dogs, oral doses of AZ liver, kidney, and spleen were observed with a NOAEL of 30 mg/kg.

Skin toxicity: Nonclinical toxicology. AZ was not reported to cause skin irritation or skin sensitization. The National Toxicology Program studied primary

irritancy and dermal sensitization to AZ in BALB/c female mice and found the treatment did not produce irritation as measured by an increase in percent ear swelling, nor was a contact hypersensitivity response demonstrated by the mouse ear swelling test or the local lymph node assay (NTP 1998). Another study by Pfizer administered AZ dihydrate to rabbits and mice and failed to demonstrate passive cutaneous anaphylaxis (Pfizer 2009).

Genotoxicity and carcinogenicity: Nonclinical toxicology. The genotoxicity of AZ has been tested in male and female CD-1 mice in bone marrow cells. No statistically significant elevation of chromosomal aberrations was reported after a single oral administration dose of 200 mg/kg, which was 20 times higher than a therapeutic dose (Riva Laboratoire Inc. 2016). This *in vivo* study indicated that AZ is not genotoxic and thus is of limited concern for carcinogenicity.

Reproductive/developmental toxicity: Nonclinical toxicology. Pfizer (2013) studied AZ in rats and mice at doses of 200 mg/kg/day that are considered moderately maternally toxic and observed no harm to the fetus due to AZ. In contrast, two fertility studies in Sprague Dawley rats suggested that AZ may cause a minimal reduction in fertility at 20 and 30 mg/kg when compared with controls, Stadnicki et al. 1996) although effects were minimal and within the historical control range. These studies suggest that azithromycin is a potential reproductive toxicant. Based on studies in rats, a LOAEL of 20 mg/kg-day was identified for a reduction in fertility as a conservative estimate of potential PoD values.

Clinical health effects summary. AZ is a commonly prescribed antibiotic that is used to treat infections caused by bacteria that lead to chronic obstructive disease and acute bacterial sinusitis (Pfizer 2013). A typical dosing regimen is a single dose of 500 mg followed by 250 mg per day for 4 days. AZ is generally a well-tolerated antibiotic, even though some cases of hypersensitivity reactions, such as angioedema, anaphylaxis, and dermatologic reactions, have been mentioned (Pfizer 2013). Pfizer (2013) reported a discontinued case of 5-day multiple-dose clinical trials in which a patient received AZ therapy. The study was discontinued due to treatment-related side effects, including nausea, vomiting, diarrhea, or abdominal pain. Pertinent clinical studies on cardiotoxicity were observed and are summarized above.

Nonclinical health effects summary. Nonclinical toxicology data are suggestive of adverse effects were identified for several endpoints as summarized above. AZ induces several target organ effects in *in vivo* toxicology studies at doses of 20, 30, and 114.6 mg/kg-day. Potential endpoints of concern for OEL derivation include effects on liver, kidney, cardiovascular, and potential reproductive effects. The effect that appears to occur at the lowest dose is potential decreased fertility with a LOAEL of 20 mg/kg-day in a study in Sprague Dawley rats.

Derivation of OELs for the specified antibiotics

The lowest therapeutic dose in humans for both CIP and AZ is 250 mg/day and was used as the PoD for deriving the ADE and sOEL (Table 1). The lowest therapeutic dose was adjusted to account for interindividual variability in susceptibility using an F_2 of 3. This value is lower than the 10-fold value often used for general population limits but is consistent with the default range used for an occupational limit setting (Dankovic et al. 2015). The reduced factor was also consistent with the use of the minimal therapeutic dose as the PoD and the long clinical use history of CIP and AZ. A factor of 3 was applied to address extrapolation from the daily therapeutic dose to potential effects with long-term exposure (F_3). This reduced factor reflects the relatively short serum half-life of CIP and AZ indicative of little dose accumulation. However, because some effects identified in the nonclinical database may increase in severity with prolonged use, a factor greater than 1 was applied. A default factor of 10 was applied for extrapolating from the minimum therapeutic dose in the absence of a clear NOAEL (F_5). An additional factor of 3 was applied to address the potential for additional effects not fully evaluated within the clinical dataset (F_4). Of importance is the potential for effects on the developing nervous system and male reproductive organs as well as the potential for inhalation route irritancy for CIP and potential cardiovascular and reproductive effects for AZ. The PoD was also adjusted for animal to human extrapolation using an F_1 of 1 since clinical data were the primary basis for the limit. The resulting composite AF_c is 270 (rounded to 300) for both CIP and AZ. The derived value resulted in an ADE of 12 μg/kg-day (Table 1). The PoD of 250 mg/day divided by the AFc of 300 and the default daily air intake of 10 m^3 yields an sOEL of 83 $\mu g/m^3$ (rounded to 80 $\mu g/m^3$) (Table 1). The derivation based on clinical doses is protective of effects observed in the

Table 1. Final selected risk values for the specified antibiotics.

References	Chemical Class	Chemical	PoD	Critical effect	Uncertainty factors	ADE	sOEL
Zimpfer et al. (2004)	Antibiotic	Ciprofloxacin	LOAEL 250 mg/day	Minimum therapeutic dose in humans	$F_1 = 1$ $F_2 = 3$ $F_3 = 3$ $F_4 = 3$ $F_5 = 10$ 300	12 μg/kg-day	80 $\mu g/m^3$
Pfizer (2013)		Azithromycin	LOAEL 250 mg/day	Minimum therapeutic dose in humans	$F_1 = 1$ $F_2 = 3$ $F_3 = 3$ $F_4 = 3$ $F_5 = 10$ 300	12 μg/kg-day	80 $\mu g/m^3$

Risk value in μg/kg-day was calculated assuming the body weight for workers for 70 kg and daily inhalation value of 10 m^3.
ADE – Acceptable daily exposure.
sOEL – Screening occupational exposure limit for inhalation exposure.
PoD – Point of departure dose.
NOEL – No observable effect level.
LOAEL – Lowest observable adverse effect level.
F_1 – Adjustment Factor for animal-to-human extrapolation.
F_2 – Adjustment Factor for human variability.
F_3 – Adjustment Factor for shorter- to longer-term exposure duration extrapolation.
F_4 – Adjustment Factor for database completeness, to address the potential for additional sensitive or severe effects.
F_5 – Adjustment Factor for extrapolation from the lowest-observed-adverse-effect level (LOAEL) to no-observed-adverse-effect level (NOEL).

nonclinical studies since OELs based on animal data were higher than the OELs based on the clinical dose.

Determination of ciprofloxacin and azithromycin in biosolids from different occupations

Table 2 shows the results of the literature survey on the amount of CIP and AZ antibiotics detected in biosolids from different media and the methodology for their extraction and detection. The antibiotics were extracted from raw sewage sludges, activated sewage sludges, digested sewage sludges, and biosolids using mainly pressurized liquid extraction (PLE), ultrasonic solvent extraction (USE), and solid-phase extraction (SPE). The antibiotics were then identified and quantified by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS), liquid chromatography fluorescence detection (LC-FLD), high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). The concentration of CIP ranged from 2.71 to 2,000 μg/kg in raw sewage sludges, from 2,300 to 3,300 μg/kg in digested sewage sludge, and from 0.044 to 3370 μg/kg in biosolids (Golet et al. 2002; Göbel et al. 2005; Lindberg et al. 2005; Chenxi et al. 2008; Walters et al. 2010; Youngquist et al. 2014; Kulkarni et al. 2017). For AZ, the concentration ranges were 0.82 to 183 in raw sewage sludge, 48 to 127 μg/kg in activated sewage sludges, 1.3 to 2.3 μg/kg in digested sewage sludges, and 13.1 to 538 μg/kg in biosolids compost (Göbel et al. 2005; Youngquist et al. 2014; Kulkarni et al. 2017).

Table 3 provides a summary of the literature survey on the concentration of total particulate matter and the calculated daily dose of inhaled biosolid aerosols by workers from different occupations handling biosolids. The particulate matter was sampled mainly for Class B biosolids using NIOSH method 0500 and a dust track aerosol monitor. In agricultural occupations, the concentration of total particulate matter ranges from 7.6 to 43 $\mu g/m^3$ during biosolids application (Paez-Rubio et al. 2007; Akbar-Khanzadeh et al. 2012). The concentration and daily dose of total particulate matter were relatively high in composting facilities with a concentration and dose ranging from 260 to 1,410 $\mu g/m^3$ and 2,600 to 14,100 μg, respectively, in personal dust samples (Epstein et al. 2001).

Table 4 provides the calculated EE of CIP and AZ from different types of biosolid sources and the calculated hazard quotient values for different occupations handling biosolids. The calculated EE of CIP ranges from 3.8×10^{-6} to 2.82×10^{-2} $\mu g/m^3$ from exposure to raw sewage sludge, 3.243×10^{-3} to 4.65×10^{-3} $\mu g/m^3$ from exposure to digested sewage sludge, and 6.2×10^{-8} to 4.8×10^{-3} $\mu g/m^3$ from exposure to biosolids (Table 4). For AZ, the calculated EE ranges from 1.12×10^{-6} to 2.58×10^{-4} in raw sewage sludge, 6.6×10^{-5} to 2.2×10^{-4} $\mu g/m^3$ activated sewage sludges, 0.2×10^{-7} to 0.4×10^{-7} $\mu g/m^3$ from digested sewage sludges, and 1.84×10^{-5} to 7.6×10^{-4} $\mu g/m^3$ from biosolids (Table 4). The calculated HQ of CIP ranges from 0.5×10^{-7} to 0.6×10^{-4} from exposure to raw sewage sludges, 0.4×10^{-4} to 0.6×10^{-4} from exposure to digested sewage sludge, and 0.7×10^{-9} to 0.6×10^{-4} from biosolids exposure (Table 4). For AZ,

Table 2. Concentration of ciprofloxacin and azithromycin found in biosolids from different media.

Reference	Compound	Media	Extraction Methodology	Detection Methodology	Amount detected (dry weight μg/kg)
Golet et al. (2002)	Ciprofloxacin	Sewage raw Sewage digested	PLE with post-extraction cleanup using SPE	LC-FLD	1,000–2,000 2,300–2,400
Spongberg and Witter (2008)	Ciprofloxacin	Biosolid from WWTP	Freeze -dried biosolid were extracted using SUE	LC-ESI-MS/MS chromatographic analysis	22.6412–46.3619
Kulkarni et al. (2017)	Azithromycin Ciprofloxacin	Sewage raw Sewage raw	Samples were extracted using Oasis HLB (60 mg) cartridges	(HPLC-MS/MS)	0.82–183 2.71–16.4
Chenxi et al. (2008)	Ciprofloxacin	Biosolid	SUE	(LC-MS/MS),	0.013(LOD) 0.044(LOQ)
Youngquist et al. (2014)	Azithromycin Ciprofloxacin	Biosolid compost Biosolid compost		LC-MS/MS	13.1–538 381–3,370
Carmosini and Lee (2009)	Ciprofloxacin	Class B Biosolid	Samples isolated by centrifuging the slurries for 1 h at 10,000 *g* and then filter sterilizing	HPLC	20–60
Walters et al. (2010)	Ciprofloxacin	Biosolid -soil mixtures in outdoor mesocosms	Ultrasonic Extraction followed by SPE	RPC MS/MS using two ion transitions per compound	542 and after 994 days of weathering 390
Lindberg et al. (2005)	Ciprofloxacin	Digested sludge	Extracted by ultrasonication	LC-MS/MS	3,300
Göbel et al. (2005)	Azithromycin	Activated sludge Digested sludges	PLE and USE	LC-MS/MS	47–158 1.3–2.3

LC-MS/MS = Liquid chromatography tandem mass spectrometry.
SPE = Solid-phase extraction; PLE = Pressurized liquid extraction.
LC-FLF = Liquid chromatography fluorescence detection.
HPLC-MS/MS = High performance liquid chromatography tandem mass spectrometry.
USE = Ultrasonic solvent extraction; SUE = Sequential ultrasonic extraction.
LOD = Limit of detection LOQ = Limit of quantification.
LC-ESI-MS/MS = Liquid Chromatography electrospray mass spectrometry/mass spectrometry positive ionization.
RPC MS/MS = Reverse phase chromatography with tandem mass spectrometry.

Table 3. Total particulate matter in the air from different occupations and the calculated inhaled daily dose.

References	Occupation	Sampling Method	Media	Airborne concentration of total particles ($\mu g/m^3$)	Inhaled daily dose of total particles (μg)
Paez-Rubio et al. (2007)	Agriculture Land	DustTrak aerosol monitor	Dewatered Class B biosolids	7.6 ± 6.3 of biosolids were aerosolized	76 ± 6.3
Low et al. (2007)	Land application site in central Arizona	N/A	Class B biosolids	Aerosols after disk incorporation and inhalable dose 15–40	150–400
Akbar-Khanzadeh et al. (2012)	Agricultural field (study field) located in northwest Ohio.	N/A	Biosolids	43 during biosolids application	430
Epstein et al. (2001)	Composting facilities	NIOSH Method 0500	Biosolids	Personal dust sampling results: 260 - 1410	2600 – 14100 for personal sampling
Bhat et al. (2013)	Field studies at a Central Arizona biosolids land application site	N/A	Biosolids	during disking 9.91–27.25	99.1 to 272.5

HQ ranges from 0.1×10^{-7} to 0.3×10^{-5} in raw sewage sludge, 0.8×10^{-6} to 0.3×10^{-5} for activated sewage sludges exposure, 0.4×10^{-8} to 0.6×10^{-6} from digested sewage sludge, and 0.2×10^{-6} to 0.9×10^{-5} from biosolids exposure (Table 4). These HQ values are far below the value of 1, often used as a benchmark for risk characterization.

Table 5 provides a summary of epidemiological studies on health outcomes associated with biosolids exposure in different occupations. The literature review of twenty-two epidemiological studies from different human waste occupations shows a significant association between workers' infection rates and exposure to human waste. The populations studied included sewage treatment plant workers, compost workers, workers in the biosolid production and/or application industry, plumbers, and gardeners. Sewage treatment plant workers were the most evaluated group. Seventeen studies have shown a significantly higher prevalence of gastroenteritis and gastrointestinal symptoms such as

Table 4. Exposure estimates (EEs) of ciprofloxacin and azithromycin in different media and hazard quotients of ciprofloxacin and azithromycin in different occupations.

Reference	Compound	Media	Amount detected (dry weight μg/kg	EEs (μg/m^3)[a]	Hazard quotient[b]
Golet et al. (2002)	Ciprofloxacin	Sewage raw	1,000–2,000	1.41×10^{-3}–2.8210^{-2}	0.2×10^{-5}–0.6×10^{-4}
		Sewage digested	2,300–2,400	3.243×10^{-2}–3.384×10^{-2}	0.4×10^{-4}–0.4×10^{-4}
Spongberg and Witter (2008)	Ciprofloxacin	Biosolid from WWTP	22–46	3.1×10^{-5}–6.5×10^{-5}	0.4×10^{-6}–0.8×10^{-6}
Kulkarni et al. (2017)	Azithromycin	Sewage raw	0.82–183	1.12×10^{-6}–2.58×10^{-4}	0.1×10^{-7}–0.3×10^{-5}
	Ciprofloxacin	Sewage raw	2.71–16.4	3.8×10^{-6}–2.3×10^{-5}	0.5×10^{-7}–0.3×10^{-6}
Chenxi et al. (2008)	Ciprofloxacin	Biosolid	0.013 (LOD)	1.83×10^{-8}	0.2×10^{-9}
			0.044 (LOQ)	6.2×10^{-8}	0.8×10^{-9}
Youngquist et al. (2014)	Azithromycin	Biosolid compost	13.1–538	1.84×10^{-5}–7.6×10^{-4}	0.2×10^{-6}–0.9×10^{-5}
	Ciprofloxacin	Biosolid compost	381–3,370	5.8×10^{-4}–4.7510^{-3}	0.7×10^{-5}–0.6×10^{-4}
Carmosini and Lee (2009)	Ciprofloxacin	Class B Biosolid	20–60	2.82×10^{-5}–8.4×10^{-5}	0.4×10^{-6}–0.1×10^{-5}
Walters et al. (2010)	Ciprofloxacin	Biosolid -	542 and after 994 days	7.64×10^{-4}	0.1×10^{-4}
			of weathering 390	5.5×10^{-4}	0.7×10^{-5}
Lindberg et al. (2005)	Ciprofloxacin	Digested sludge	3300	4.65×10^{-3}	0.6×10^{-4}
Göbel et al. (2005)	Azithromycin	Activated sludge	47–158	6.6×10^{-5}–2.2×10^{-4}	0.8×10^{-6}–0.3×10^{-5}
		Digested sludges	1.3– 2.3	1.8×10^{-6}–3.24×10^{-6}	0.2×10^{-7}–0.4×10^{-7}

[a]Exposure estimates in μg/m^3 calculated using Equation 3 and airborne concentration of total particles reported by Epstein et al. (2001).
[b]Derived using Equation 4 with the derived OELs for ciprofloxacin or azithromycin, as appropriate.

abdominal pain, pyrosis, stomachache, abdominal pain, dyspepsia, ructus; an increased risk of intestinal parasite carriage such as whipworm, Giardia lamblia, Entamoeba coli and Endolimax nanus, and a significantly increased number of tropheryma whipplei which is Whipple disease agent (Morse et al. 1979; Scarlett-Kranz et al. 1987; Brugha et al. 1998; Rylander 1999; Schlosser et al. 1999; Trout et al. 2000; Weldon et al. 2000). A significantly higher prevalence of toxoplasma gondii infection was found in plumbers, gardeners, and construction workers highly exposed to water, sewage, and soil and living in suburban areas (USEPA 1994). Epidemiological studies of compost workers have shown significantly more symptoms and diseases of the airways and skin on compost workers than controls. More frequent eye and skin irritation among compost-exposed groups were observed (Alvarado-Esquivel et al. 2010; Heldal et al. 2015). The health effects seen on these different workers are caused mainly by bacterial (Brugha et al. 1998; Van Hooste et al. 2010), viral (Rylander 1999), and protozoan infections (Schlosser et al. 1999).

Discussion

Understanding the health effects in biosolid-exposed workers is becoming a priority in public and occupational health due to the widespread production, application, and use of biosolids and the likelihood of workplace exposure to pathogens and pharmaceuticals.

Publicly available OELs from regulatory agencies and known organizations that set OELs are typically preferred for characterizing risks from exposure and for developing strategies for implementing adequate controls to protect the workplace. This reflects the availability of documentation of the OEL basis rationale and the inclusion of peer review systems used by such organizations. However, the absence of these health-based limits for many substances, including most drug substances, has led drug manufacturers to derive their own OELs to ensure the protection of workers in pharmaceutical manufacturing. The derived sOEL of 80 μg/m^3 for AZ was somewhat below the 8-h time-weighted average OEL of 500 μg/m^3 from the manufacturer's SDS. As for CIP, the calculated sOEL of 80 μg/m^3 was similarly lower than the CIP time-weighted average OEL of 600 μg/m^3 found in the manufacturer's SDS (Pfizer 2015, 2018). It is not possible to attribute a basis for these divergent OELs for CIP since the manufacturer's SDS does not provide a rationale for their OEL derivation. However, in many cases, drug innovators maintain direct health effects data that can inform the OEL derivation that is not available to the public. Such data could affect PoD selection as well as the assignment of AFs. The sOELs calculated for the current assessment are above the OELs of 11 μg/m^3 derived by Schwab et al. (2005) which was from a published ADI based on the bacterial minimum inhibitory concentration as a PoD. This discrepancy appears to be related to the selection of target efficacy as the critical effect. The OELs applied for this screening risk assessment are consistent with expectations—somewhat below the manufacturers' OELs and above the limit derived by Schwab et al. (2005) based on the bacterial effect that might be not associated with clear human adversity.

Data from the literature on airborne concentrations of total particulate matter in different biosolids

Table 5. Epidemiological studies in different occupations handling biosolids.

Occupation	Study Design	Heath Outcome	References
Sewage Treatment Plant Workers	Cross-sectional	Nasal irritation, tiredness, and diarrhea were significantly higher in sewage workers compared with controls.	Rylander (1999)
Sewage Treatment Plant Workers	Cross-sectional	Antibodies to hepatis A virus were detected in 28.4% of wastewater workers and in 23.6% of drinking-water workers.	Weldon et al. (2000)
Water and sewage workers	Cross-sectional	60% of workers reporting exposure to raw sewage had hepatis A virus infection.	Brugha et al. (1998)
Sewage Treatment Plant orkers	Cross-sectional	Out of 145 sewage treatment plant workers: 85 (59%) had noted eye irritation, 65 (45%) had headaches, and 39 (27%) had throat irritation.	Morse et al. (1979)
Sewage Treatment Plant Workers	Cross sectional	Fifty-nine (20%) of 302 participants tested positive for anti-Hepatitis A Virus (HAV). Forty-two wastewater workers and 17 control workers tested positively for antibodies of -HAV, even though no association was found between wastewater work and an increased prevalence of anti-HAV after controlling for confounding effects of age and race.	Trout et al. (2000)
Compost workers	Cross sectional	151 data sets including 58 compost workers, 53 biowaste collectors, and 40 control subjects were analyzed. 22 compost workers had up to three health complaints compared with only three biowaste collectors, and one control subject. Compost workers had a significantly higher prevalence of tracheobronchitis. Mucous membrane irritation, sinusitis, eczema, dermatomycosis, pyoderma, and otitis externa significantly more symptoms and diseases of the airways ($p = 0.003$) and skin ($p = 0.02$) were reported by compost workers than controls.	Bünger et al. (2000)
Compost workers	Cross sectional	Eye and skin irritation were reported more frequently among compost-exposed groups. Compost workers had greater IgG antibody levels against compost-derived endotoxin, elevated C3 and hemolytic complement levels, and higher white blood-cell and eosinophilic counts	Clark et al. (1984)
Sewage Treatment Plant Workers	Cross sectional	The prevalence mean of intestinal parasite carriage was 11.8% (57/480), related to the presence of protozoa in 91% of samples. G. lamblia was present in 3.5% (17/480) of samples. The incidence of positive parasitological stool examination was 5.9/100 person-years. The incidence of G. lamblia in stool examinations was 1.7/100 person-years.	Schlosser et al. (1999)
Sewage Treatment Plant Workers	Cross sectional	The frequency of headache, dizziness, sore throat, skin irritation, and diarrhea was significantly higher among the sewage workers.	Scarlett-Kranz et al. (1987)
Sewage Treatment Plant Workers	Cross sectional	Serological confirmation of Pontiac fever in all five workers and recovery of *Legionella pneumophila* from sewage sludge.	Gregersen et al. (1999)
Sewage Workers	Multiple cross-sectional survey	an increased risk of intestinal parasite carriage such as whipworm, *Giardia lamblia,* Entamoeba coli and Endolimax nanus.	Schlosser et al. (1999)
Wastewater Treatment Workers	Cross sectional	Significantly higher prevalence of gstroenteritis, gastrointestinal symptoms specifically abdominal pain, and headaches	Khuder et al. (1998)
Sewage workers	Cross sectional	Plasma triglyceride concentrations were found to increase with serum PCB concentrations, suggesting that PCBs might alter lipid metabolism.	Baker et al. (1980)
Sewage treatment plants workers	Cross sectional	*Tropheryma whipplei* (Whipple disease agent) was found significantly more often in stool of workers exposed to sewage water.	Schöniger-Hekele et al. (2007)
Wastewater Treatment worker	Prospective	Statistically significantly higher gastrointestinal illness between newly employed workers and the other groups.	Clark et al. (1979)
Sewage treatment plants workers	Cross sectional	Skin disorders, diarrhea, and other gastrointestinal symptoms were significantly greater among sewage-treatment workers.	Lundholm and Rylander (1983)
Sewage treatment plants workers	Cross sectional	Elevations in IgA, thrombocytes, leukocytes, and endotoxin antibodies.	Rylander et al. (1997)
Workers in Biosolids Production and/or Application Industry	Cross sectional	History of gastrointestinal illness among workers; enteric bacteria were detected in the air and bulk samples.	Burton and Trout (1999)

(*Continued*)

Table 5. Continued.

Occupation	Study Design	Heath Outcome	References
Sewage workers at WWTP	Cross sectional	The prevalence of gastrointestinal symptoms such as pyrosis, stomachache, abdominal pain, dyspepsia, and ructus was higher among the sewage workers.	Van Hooste et al. (2010)
Plumbers, Gardener & construction workers	Cross-sectional	The prevalence of *T. gondii* infection was significantly higher in workers without education living in suburban areas.	Alvarado-Esquivel et al. (2010)
Sewage Treatment Plant Workers	Cross sectional	The most common symptoms reported by workers included cough, sputum production, wheezing, sore throat, and skin complaints.	Nethercott and Holness (1998)
Compost and sewage dust workers	Cross-sectional	The higher concentrations of fibrinogen and CRP in exposed workers compared to the referents may reflect a low-grade systemic inflammation	Heldal et al. (2015)

occupations were used to calculate the airborne exposure for these two antibiotics. The total concentration of airborne particles reported by Epstein et al. (2001) was chosen for the calculation of the EEs because it has the highest published value and was obtained using a personal dust sampler. It was found that the EE of CIP ranges from 6.2×10^{-8} to $3.4 \times 10^{-2}\,\mu g/m^3$ in various phases of biosolid treatment. For AZ, the respective range is 1.8×10^{-6}–$7.6 \times 10^{-4}\,\mu g/m^3$. The results show that the amounts of these two antibiotics in the worker's breathing zone are likely to be too low to cause adverse side effects as a result of occupational inhalation exposures. These findings were confirmed by the HQ results. The calculated HQ for CIP ranges from 0.004 to 0.7×10^{-9} in various phases of biosolid treatment. For AZ, the HQ ranges from 0.4×10^{-7} to 0.3×10^{-5}. These HQ values are far below the value of 1 which is often used as a benchmark for risk characterization. These results suggest no adverse health effects are expected from direct inhalation exposures to CIP or AZ for workers handling biosolids due to antibiotic exposure.

This assessment is limited to inhaled exposures, and thus contributions from dermal route exposures should also be considered as a potential contributor to the exposure to these antibiotics. Data on dermal absorption of these antibiotics were not identified; however, *in silico* dermal penetration estimates could be developed to aid in screening risk assessment. Dermal exposure can also generate increased oral doses (WHO 2020) and hand-to-mouth transfer can be a relevant source of exposure in occupational settings.

To date, there are no published biomonitoring studies that have considered these two antibiotics or their metabolites in blood or urine samples taken from workers. Since air sampling does not consider routes of exposure other than inhalation, it would be useful to conduct a biomonitoring study of these two antibiotics in biosolids-exposed workers. It is also important to determine whether there is a correlation between the biomonitoring and the air sampling results of these two antibiotics as a basis for risk assessment using absorbed or internal dose-based. OELs. This reflects the potential for exposure from multiple routes and the growing emphasis on risk assessment for consideration of aggregate and cumulative risks (Lentz et al. 2015).

The study was initiated as part of a larger effort to understand the implications of antibiotic exposures for the observed prevalence of microbial-related illness among workers handling biosolids. One overarching concern was that the combination of direct antibiotic exposure in the workplace coupled with exposure to bacteria that have obtained antibiotic resistance (due to routine presence in human waste streams) might be enhancing the risk of workers in this industry. A prior study showed that the concentrations of these antibiotic-resistant bacteria were not negligible in WWTPs and may represent an exposure pathway for some workers (Niang et al. 2023). Additional studies on the combined impacts of these exposures are expected to shed additional light on the health implications of exposure to antibiotics in biosolids workers.

Limitations

The major limitation of this study is that the derived health-based sOEL values were designed to guide the protection of most workers against direct pharmacology and any adverse side effects of these drugs as a result of occupational exposure. They are not explicitly designed to prevent the development of potential antibiotic resistance. Hence, there may be a further need for health-based limits to protect workers from the emergence of resistant pathogens and changes in gut microflora. Another limitation of this study is that the total particulate matter reported by Epstein et al. (2001) is used to calculate the EEs. This personal dust sampling study at a biosolids composting facility is

not likely to be representative of all the biosolid-exposed occupations, and therefore, the results might not be generalizable to other workplaces such as the WWTP. Thus, although the amounts of CIP and AZ in these occupations were well below the OELs and likely too low to cause direct CIP and AZ-related adverse health effects, inhalation exposures to these two antibiotics could be quantified in field studies to verify the EEs.

Conclusion

This study was conducted as a screening level risk characterization for direct effects of CIP and AZ exposures among workers who handle biosolids. Although the estimated inhalation exposure concentrations of CIP and AZ in the breathing zone for these occupations were well below the traditional OELs and likely too low to cause adverse health effects, additional exposure considerations need to be evaluated. The dermal route should be considered as a potential contributor to antibiotic exposures in WWTPs. In addition, the health risk impacts of antibiotic resistance need further study. It is prudent to maintain the use of precautionary controls to limit exposure to human waste while working to better understand the antibiotics and pathogens present in waste material and the relative source contributions for each route of exposure.

Disclosure statement

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ORCID

Mamadou Niang http://orcid.org/0000-0002-1332-7681
Tiina Reponen http://orcid.org/0000-0002-7987-4901

Data availability statement

De-identified data will be available upon request and approval by the corresponding author.

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