Assessment of the presence of pharmaceuticals in, and removal from, municipal wastewater in Aotearoa New Zealand

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DISCLAIMER

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ABBREVIATIONS/GLOSSARY

ADI	acceptable daily intake
API	active pharmaceutical ingredient
ATSDR	Agency for Toxic Substance and Disease Registry
CECs	contaminants of emerging concern
E1	estrone
E2	17β-estradiol
E3	estriol
ECs	emerging contaminants
EE2	17α-ethinyl estradiol
EFSA	European Food Safety Authority
EOCs	emerging organic contaminants
EPs	emerging pollutants
HBGV	health-based guidance value
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MED	minimum therapeutically-effective dose
MTD	maximum tolerated dose
NSAIDs	non-steroidal anti-inflammatory drugs
OECD	Organisation for Economic Cooperation and Development
OTC	over-the-counter
PPCPs	pharmaceutical and personal care products
QMRA	Quantitative Microbial Risk Assessment
TDI	tolerable daily intake
TTC	threshold of toxicological concern
TUI	tolerable upper intake
UNEP	United Nations Environment Programme
US EPA	United States Environmental Protection Agency
UV	ultra-violet
WHO	World Health Organization
WWTP	wastewater treatment plant

EXECUTIVE SUMMARY

Pharmaceuticals are a large and diverse group of biologically-active compounds developed for the diagnosis, treatment, management and prevention of various health conditions. Their obvious benefits to human and animal health means they are used extensively; an estimated 4,000 active pharmaceutical ingredients (APIs) are administered globally as prescription medications, over-the-counter (OTC) therapies and veterinary medicines, with consumption rates forecast to increase rapidly in the near future. However, such usage has resulted in pharmaceuticals being increasingly detected as contaminants in surface waters, groundwaters, sediments and soils, prompting concerns as to their potential effects on human and environmental health. The primary route by which pharmaceuticals enter the environment is through municipal wastewater effluents. Typically, the administered dose is not completely absorbed or metabolised within the patient's body, and significant fractions may be excreted in urine and/or faeces into the wastewater network. Improper disposal of unwanted medications down the toilet or sink, or effluents from pharmaceutical manufacturing or research facilities may also be sources. Conventional wastewater treatment plants (WWTPs) are not specifically designed to remove pharmaceutical residues from wastewater, and a substantial amount of some pharmaceutical compounds may therefore pass through the WWTP to be discharged in treated effluents to the environment.

The aim of this report is to improve our understanding of the potential risks that the environmental presence of these contaminants may pose to human health in Aotearoa New Zealand. To do so, we reviewed the available literature to determine the presence of pharmaceuticals in New Zealand municipal wastewater, and the efficacy of the wastewater treatment processes commonly used in New Zealand WWTPs in removing those compounds. Subsequently, the data was entered into an exposure assessment model, to estimate the potential human health risks associated with exposure to pharmaceuticals during recreational use of aquatic environments impacted by wastewater discharge.

Relatively little data was available on the presence of pharmaceuticals in wastewater in Aotearoa New Zealand; there were few studies publicly available, most of which focused on a small number of pharmaceutical analytes from a small number of samples (often one or two samples from a single WWTP). The available data determined that at least 57 different pharmaceuticals (including 2 metabolites) have been detected in either untreated influent and/or treated effluent; 23 of these are among the 100 most highly-prescribed pharmaceuticals in New Zealand (based on dispensing frequency). Although likely biased by their being among the most commonly-targeted analytes, the APIs most frequently reported as being detected in wastewater were the analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) acetaminophen, diclofenac, ibuprofen and naproxen; the antibiotics sulfamethoxazole and trimethoprim; the anticonvulsant carbamazepine; beta blockers including atenolol and metoprolol; psychiatric medications including fluoxetine; the anti-hypertensive diltiazem; and steroid hormones estrone and 17α-ethinyl estradiol. Where quantifiable levels of pharmaceuticals were detected, concentrations ranged from several ng/L to tens of µg/L; in most cases, concentrations tended towards tens to hundreds of ng/L. A further 32 pharmaceuticals were inferred as being present in New Zealand wastewater by virtue of their presence in environmental samples (surface water, marine and estuarine sediments, groundwater and biowaste), where the most plausible explanation for their

presence was wastewater-related contamination. Overall, the available data suggests that the types and concentrations of pharmaceuticals in wastewater in Aotearoa New Zealand are consistent with reports from overseas; it would seem reasonable therefore, that many of the additional pharmaceuticals detected in international studies may also be present to some extent in New Zealand wastewaters. There is insufficient data available to draw conclusions regarding trends around seasonal presence (although total pharmaceutical load may be higher in winter) or the roles of local factors that may influence the presence and/or removal of compounds, such as the size or demographics of a community served by a given WWTP, local climate or the treatment processes and operating parameters of the WWTP.

The fate of different pharmaceuticals through a WWTP is highly dependent on their physicochemical characteristics, the type of treatment processes used and various operational parameters. Removal efficiencies can vary significantly for different compounds, as well as for the same compound under different treatment conditions. Only two New Zealand studies were identified in which the removal of pharmaceuticals from wastewater were investigated; both studies involved WWTPs utilising activated sludge systems, with one also treating ~25% of wastewater flow through a membrane bioreactor. Ibuprofen, salicylic acid, 17α-ethinyl estradiol, acetaminophen, naproxen, clarithromycin and roxithromycin were relatively well removed (approximately >85%), with moderate removal rates for diltiazem, sulfamethoxazole, fluoxetine and atenolol (>60%). Diclofenac, trimethoprim and metoprolol were poorly removed (<35%), with carbamazepine showing almost no removal. In the absence of further information on removal in the New Zealand context, a brief overview of removal rates observed for selected pharmaceuticals in various international studies is included. Waste stabilisation ponds and conventional activated sludge – the most common wastewater treatment processes used in NZ – appear to have mixed removal efficacy, with good removal of some contaminants and poor to nil removal for others; many contaminants appear to be removed by less than 50%. More advanced techniques such as advanced oxidation or ultrafiltration can improve the removal rates of many pharmaceuticals, but are not routinely used in WWTPs due to their high implementation and operational costs.

A Tier 1 screening-level assessment was carried out to estimate the potential human health risks associated with exposure to 28 representative pharmaceuticals during recreational use of wastewater-impacted environments. Given the dearth of publicly available toxicological data for most pharmaceuticals and the lack of studies assessing the effects of chronic exposure to sub-therapeutic concentrations, the assumptions of the assessment were set conservatively, and a threshold of toxicological concern (TTC) approach was used to set health-based guidance values (HBGVs). The exposure assessment indicated that exposure levels for each API were below their respective HBGVs by several orders of magnitude, and that there is no appreciable risk to people's health as a result of possible exposure to pharmaceuticals during swimming, surfing canoeing/kayaking, rowing, sailing or fishing. The assessment does not include exposures resulting from contaminated drinking-water or mahinga kai. Risks were assessed based on exposure to individual pharmaceuticals, rather than multiple compounds at the same time, as is more likely to occur with environmental exposure; in the absence of detailed understanding of the interactions between many APIs and their potential to cause additive, synergistic or antagonistic effects, there is currently no agreed approach as to how complex pharmaceutical mixtures should be assessed. The exposure assessment is not applicable to risks to ecological health and aquatic organisms, which are assessed against very different threshold values.

1. INTRODUCTION

1.1 BACKGROUND

Wastewaters can contain a myriad of microbiological and chemical contaminants that may present a risk to public health, particularly where they are discharged to receiving environments without treatment (eg, as spills and overflows or unconsented discharge) or where treatment has not been effective in removing certain contaminants. People may then be exposed to those contaminants when they interact with the receiving environment, for example, as a drinking-water source, during swimming or other recreational activities, or the collection and consumption of mahinga kai.

Recently, several reviews have been prepared for Health New Zealand | Te Whatu Ora that provide an overview of the diversity of contaminants that may be present in municipal wastewater, urban stormwater and trade wastes, and the adverse human health outcomes that may be associated with exposure to those contaminants (Eaton 2022; Coxon and Eaton 2023; Eaton and Coxon 2023). These reviews were based on international literature and focused on untreated effluents, since different treatment processes show significant variation in their abilities to remove different types of contaminants, as well as to provide insight into the contaminants potentially present in 'worst case scenarios' of overflow or treatment failure. In addition, an exposure assessment tool has been developed that can be used to estimate the risks associated with exposure to chemical contaminants during recreational use of waterways that might be impacted by wastewater or stormwater discharge (Cressey 2023). This tool complements the approach to modelling the risk of infection and illness caused by pathogenic microorganisms, known as a Quantitative Microbial Risk Assessment (QMRA) (WHO 2016).

The next stage in better understanding the risk that these contaminants may pose to public health in Aotearoa New Zealand involves a detailed assessment of the presence of these contaminants in New Zealand wastewaters, and the efficacy of treatment processes commonly used in New Zealand in removing these contaminants. This will provide a more representative picture of the concentrations of contaminants potentially being discharged to receiving environments. This, in turn, will provide more robust inputs to the exposure assessment tool to better estimate the potential risk to people interacting with those environments. Due to the breadth of different contaminants that have been identified as being present in wastewater, this current report will focus on a single group: pharmaceuticals.

1.2 PHARMACEUTICALS IN WASTEWATER

1.2.1 What are pharmaceuticals?

Pharmaceuticals are a large and diverse group of biologically-active compounds with important use in the diagnosis, treatment, management and prevention of various health

conditions (Daughton and Ternes 1999; Adeleye et al. 2022). They may also be referred to as medicines or drugs, and take a variety of forms including pills, tablets or liquids for ingestion, creams or ointments for topical applications, vapours for inhalation, or solutions for injection. Pharmaceuticals are an invaluable commodity to society, and their beneficial effects on human health and longevity, animal health, food production and economic welfare are widely acknowledged (Burns et al. 2018; OECD 2019). As such, global use of pharmaceuticals continues to increase rapidly – approximately 4,000 active pharmaceutical ingredients (APIs) are administered worldwide as prescription medications, over-the-counter (OTC) therapies and veterinary medicines, with some 100,000 tonnes of APIs produced globally every year (OECD 2019; UNEP 2019).

The chemical structure and properties of pharmaceutical compounds vary widely, as do their applications; to facilitate their study, they are often grouped according to their pharmacological effect and/or their therapeutic action, for example, as antibiotics, analgesics, beta blockers, non-steroidal anti-inflammatory drugs (NSAIDs), antiepileptics, blood lipid-lowering agents, antidepressants, hormones or antihistamines, although compounds within the same therapeutic class can have quite different structures and modes of actions to each other (Daughton and Ternes 1999).

Pharmaceuticals and personal care products[1] (PPCPs) are one of the largest groups of emerging contaminants (ECs) (Reyes et al. 2021). There are multiple definitions for ECs and several related and largely interchangeable terms that are also used to describe the group, including emerging pollutants (EPs), micropollutants, contaminants of emerging concern (CEC) and emerging organic contaminants (EOCs), since many chemical ECs are organic in nature (Stewart et al. 2016). Essentially, ‘emerging contaminants’ describes any synthetic or naturally-occurring chemical or microorganism that is not currently regulated or routinely monitored in the environment (though may be a candidate for future regulation), and has the potential to enter the environment and cause known or suspected adverse ecological and/or human health effects. Emerging contaminants include both newly designed chemicals and pollutants that have been present in the environment for some time, but whose presence and/or significance has only recently been recognised or evaluated (US EPA 2008; Stewart et al. 2016).

1.2.2 Pharmaceuticals in the environment as an emerging concern

The extensive and widespread use of pharmaceuticals results in their continuous release to the environment, and they are increasingly being reported as environmental contaminants. Trace levels of pharmaceuticals (eg, in the sub-ng/L to low µg/L range) have been widely reported in surface waters, groundwater, drinking-water, wastewater and soil (Kolpin et al. 2002; Boyd et al. 2003, 2004; Kasprzyk-Hordern et al. 2009; WHO 2012; aus der Beek et al. 2016; Peake et al. 2016; Burns et al. 2018; OECD 2019; Reyes et al. 2021; Adeleye et al. 2022). For example, PPCPs were present in more than 40% of the 139 streams sampled during a nationwide study in the USA (Kolpin et al. 2002), and several reviews have noted that more than 990 unique APIs have been detected in environmental samples worldwide

[1] Personal care products are products that are applied topically to the body to promote overall health and wellbeing, such as soaps, shampoos, moisturisers, toothpastes, sunscreens, deodorants, insect repellents, sunscreens, sanitisers and cosmetics. They contain compounds including antiseptics, fragrances, parabens, phenols and UV filters, and are often investigated together with pharmaceuticals (ie, as the group ‘pharmaceuticals and personal care products,’ PPCPs).

(aus der Beek et al. 2016; Reyes et al. 2021; Oldenkamp et al. 2024). The presence of pharmaceuticals in the environment has been highlighted as an emerging concern for human and environmental health, both globally (UNEP 2019) and in New Zealand (PCE 2022), however, our understanding of the presence of many APIs in the environment, and moreover, their transformation or degradation products, environmental fate and potential impact on human and environmental health, remains limited (OECD 2019).

Concerns regarding the potential impacts of pharmaceuticals in the environment arise primarily from the fact that pharmaceutical compounds have been specifically designed to interact with biological receptors and systems to produce a physiological response or exert toxic effects (eg, to infectious microorganisms), and further, to be potent at low doses (Khetan and Collins 2007; WHO 2012; Vasquez et al. 2014; Peake et al. 2016; Reyes et al. 2021; Adeleye et al. 2022). In addition, many pharmaceuticals are designed to be stable to ensure they reach and interact with their biological targets, which means they often degrade slowly in the environment (OECD 2019), although even compounds that do break down rapidly can show 'pseudo-persistence' by virtue of their high usage and continuous input into the environment (Daughton and Ternes 1999; Schwarzenbach et al. 2006; Reyes et al. 2021). An estimated 30% of pharmaceuticals have a high lipid solubility, allowing them to bioaccumulate within food chains (Khetan and Collins 2007). Finally, the breadth of pharmaceuticals in use and being detected in the environment means there is significant potential for exposure to mixtures of compounds that may have similar mechanisms of action or act upon the same target, and therefore have potential for additive or synergistic effects beyond what might be suggested by considering the presence of a compound in isolation (Schwarzenbach et al. 2006; Khetan and Collins 2007; Vasquez et al. 2014).

Adverse effects of exposure to pharmaceuticals have been documented in animals, both in laboratory studies and in wildlife, showing that despite their potential benefits, APIs can also cause undesirable changes in physiology, behaviour and reproduction, and in some cases, can cause mortality (Oaks et al. 2004; Liney et al 2006; Scholz and Klüner 2009; Mennigen et al. 2011; Larsson et al. 2014; Brodin et al. 2017; OECD 2019). The potential risks to human health from environmental exposure to pharmaceuticals are much less clear, and while some effects are suspected, more research is needed (Wang et al. 2016). The concentrations of pharmaceuticals reported in the environment are typically orders of magnitude lower than those prescribed as therapeutic doses, so that the risk of acute toxicity is unlikely (Khetan and Collins 2007; WHO 2012; Larsson et al. 2014; Cressey 2018). However, the potential for adverse human health effects from chronic exposure to low concentrations of APIs cannot be excluded, due to a lack of data addressing such exposures and the potential for different toxicodynamics for acute and chronic exposures to limit extrapolation from short-term studies (Khetan and Collins 2007). Moreover, therapeutic use describes a situation of intentional use (usually ingestion) by an individual in order to attain a specific benefit or therapeutic effect. However, many pharmaceuticals have potential for adverse side effects or are contraindicated with other pharmaceuticals, health conditions or certain sub-populations. Thus, the potential risks associated with the unintended, chronic exposure of vulnerable or non-target sub-populations (eg children, pregnant women, individuals with allergies or sensitivities, non-target gender groups), exposure to genotoxic compounds such as antineoplastics (anti-cancer drugs), chronic exposure to compounds intended for short-term usage or exposure to mixtures of APIs cannot be discounted (Khetan and Collins 2007; Kumar et al. 2010; Vaquez et al. 2014; Cressey 2018).

1.2.3 Sources of pharmaceuticals in municipal wastewater

Municipal wastewaters are the major contributor to pharmaceutical contaminant loads in the environment (Khetan and Collins 2007; aus der Beek et al. 2016; Reyes et al. 2021; Adeleye et al. 2022). The primary route by which pharmaceuticals enter the wastewater network is as a result of patient excretion: following ingestion, APIs undergo metabolic reactions within the body that may include oxidation, hydroxylation, cleavage or glucuronidation. However, significant fractions of the administered dosage are not completely metabolised and are therefore excreted – either as the unmetabolized parent compound, conjugates, and/or bioactive metabolites – in urine or faeces and thus into the wastewater network (Khetan and Collins 2007; Reyes et al. 2021; Adeleye et al. 2022). Depending on the specific pharmaceutical, an estimated 30 to 95% of the administered oral dose is excreted unmetabolised (Castiglioni et al. 2006; OECD 2019); for example, some fluoroquinolone and tetracycline antibiotics, beta blockers, and antidiabetics (especially metformin) are commonly excreted unchanged, while different analgesics undergo varying degrees of metabolism (Adeleye et al. 2022).

Improper disposal of unwanted or expired pharmaceuticals[2] to the wastewater network may also be a source of pharmaceuticals in wastewater (Khetan and Collins 2007). For example, in a survey of New Zealanders on the disposal of unwanted or expired medications, 55% of respondents said they disposed of liquid medications by pouring them down the sink or flushing them down the toilet, with 19% disposing of solid medications (ie, pills and capsules) in this way (Braund et al. 2009). A similar survey of New Zealand community pharmacies found that the most common means of disposing of unwanted liquid medications (52% of respondents) or Class B controlled drugs (73% of respondents) was also to put them down the sink or toilet (Tong et al. 2011). Whilst New Zealand data suggests a significant proportion of unwanted medications may be disposed of via the wastewater network, such disposal is generally considered to be a minor pathway for pharmaceuticals to wastewater when compared with patient excretion (Castiglioni et al. 2006; Khetan and Collins 2007; Reyes et al. 2021).

Effluents from pharmaceutical manufacturing facilities, hospitals, animal care facilities or research institutes may be a further source of pharmaceuticals to municipal wastewater (Larsson et al. 2014; Scott et al. 2018; Adeleye et al. 2022). High concentrations of pharmaceuticals (eg, mg/L range) are reported in the effluents from pharmaceutical manufacturing or formulation facilities in India, China, Pakistan, Korea, Taiwan, the USA and parts of Europe; the effluents from one WWTP receiving wastewater from 90 manufacturing facilities in India were found to contain up to 31 mg/L of the antibiotic ciprofloxacin (Larsson et al. 2014). Whilst these facilities are not likely to be important sources of pharmaceuticals for many wastewater catchments, they may be significant on a local scale. For example, studies of the final effluents from municipal WWTPs in the USA have found that WWTPs receiving effluents from pharmaceutical manufacturing or formulating facilities can contain concentrations of some APIs 10 to 1,000 times higher than WWTPs not receiving such effluent (Phillips et al. 2010; Scott et al. 2018).

[2] Reasons for having unwanted medications can include a patient's condition having improved or resolved, a change of medication or dose, medication causing side effects, excess supply, unclear instructions, or bereavement (Braund et al. 2009; James et al. 2009).

1.2.4 Removal of pharmaceuticals from wastewater by treatment processes

Conventional wastewater treatment plants are not specifically designed to treat or remove pharmaceuticals, thus a substantial amount of some compounds pass through to receiving environments (Verlicchi et al. 2012; Luo et al. 2014; Margot et al. 2015; OECD 2019; Reyes et al. 2021; Adeleye et al. 2022). For example, a review of pharmaceuticals in the effluents from WWTPs in the UK found that 13% of all WWTPs had pharmaceuticals in their effluents at concentrations high enough to have potential for adverse environmental impacts (Comber et al. 2018). A study of effluents from 50 large WWTPs in the USA found that of 56 APIs analysed, ten were present in more than 80% of effluents sampled (Kositch et al. 2014).

A rapidly growing body of data shows that the removal of pharmaceutical compounds from wastewater will be influenced by the treatment process(es) employed at the WWTP, and various operational and environmental factors. Further, the removal efficacy of different treatment processes can differ significantly for different APIs, due to the different physicochemical properties of individual compounds (Wang and Wang 2016; Reyes et al. 2021; Adeleye et al. 2022). As such, removal rates for different compounds are highly variable, with removal efficiencies spanning the full range from 0 to 100%, though rates between 20 and 80% are most commonly reported (aus der Beek 2016). There are also instances where ‘negative removal’ of certain compounds is reported; this may happen, for example, when conjugated metabolites present in influent wastewater are deconjugated by microorganisms during biological treatment processes, leading to a higher relative concentration of the parent compound in treated effluents (Kumar et al. 2019).

1.2.5 Future trends and the need to address knowledge gaps

Estimating the potential risks to human and/or ecological health requires characterising the occurrence of pharmaceuticals in various environmental compartments (Kositch et al. 2014; Reyes et al. 2021). Despite the emerging interest of the scientific community and development of policy-level strategy in some jurisdictions, there remain significant knowledge gaps (Reyes et al. 2021). Key among these is that only a relatively small number of pharmaceutical compounds in use have been tested for in different environmental samples, including wastewater (Burns et al. 2018). Most studies investigate only handful of pharmaceutical analytes, usually those with the highest consumption rates within a community or within a particular class of compounds (eg hormones); for many APIs, including many that are widely prescribed, there is no data on environmental occurrence (Kositch et al. 2014; Reyes et al. 2021). In addition, a lack of analytical standards means there are very few cases in which the presence of intermediate compounds (ie, human metabolites or treatment/degradation intermediates or products) is assessed, raising questions as to the potential ecotoxicological or human health risk of these compounds that may still possess bioactive structural elements (Peake et al. 2016).

Concerns regarding the presence of pharmaceuticals in the environment are likely to grow, with global pharmaceutical use expected to increase significantly in the future. For example, pharmaceutical use in Germany is forecast to increase 43-67% by 2045 compared with a 2015 baseline (OECD 2019), and use in the UK is projected to double by 2052 (Burns et al. 2018). Key drivers of increasing pharmaceutical use include an increasing and aging population; increasing welfare standards, particularly in growing and emerging economies where there is an increasing ability to treat age-related and chronic disease; increasingly

urbanised environments improving access to pharmaceuticals; evolution of clinical practices that result in earlier treatment, higher doses or prolonged treatments; intensification of agriculture and aquaculture practices; development of new pharmaceuticals; and increasing need for pharmaceutical use to managing increasing rates of non-communicable, vector-borne, waterborne and respiratory diseases relating to climate change (Khetan and Collins 2007; Burns et al. 2018; OECD 2019; UNEP 2019). On the other hand, improved preventative medicine, improved access to sanitation systems, developments in wastewater treatment processes and advances in pharmaceutical design that increase human absorption and metabolism might help to mitigate some of these concerns (Burns et al. 2018).

Although there have been no direct demonstrations of human health impacts, more research in this area is required (Wang et al. 2016; Burns et al. 2018; Sengar and Vijayanandan 2022). It would therefore seem prudent to improve our understanding of the sources, presence and fate of pharmaceuticals in the environment, the potential risk of unintentional exposure to these compounds, and how these risks may be amplified (or conversely, reduced) by changes in usage, management and/or climate (Burns et al. 2018).

1.3 APPROACH AND SCOPE

The objective of this report is to assess the presence of pharmaceuticals in New Zealand municipal wastewater, and the efficacy of the most commonly-used treatment processes in removing those compounds. The report will focus on 'non-hospital' pharmaceuticals – that is, pharmaceuticals (both prescription and over-the-counter) that are widely administered and consumed in the community, as opposed to those administered predominantly within a hospital setting. Guided by international literature and New Zealand-specific data on pharmaceutical dispensing and environmental sampling, the review will cover the following aspects:

- A review of the available literature (scientific publications, technical reports, monitoring or consent-related sampling data) on the presence of pharmaceuticals in New Zealand municipal wastewaters.
- A review of the available literature on the efficacy of different wastewater treatment processes in removing the identified pharmaceutical compounds, with a focus on those processes most commonly used in New Zealand WWTPs.
- Subject to the availability of data, utilisation of the exposure model developed by Cressey (2023) to estimate the potential human health risks associated with exposure to representative examples of the identified pharmaceutical compounds in a number of scenarios involving recreational use of receiving waters.

The following considerations are outside of the scope of the current review:

- Wastewaters other than municipal wastewater. While municipal wastewater may contain inputs of stormwater, trade wastes/industrial effluents and hospital effluents, the presence of pharmaceuticals in, or their removal from, these matrices will not be specifically considered here.

- The presence of, or health risks that may be associated with, the presence of pharmaceutical compounds in biosolids.
- The presence of, or health risks that may be associated with, the presence of personal care products (eg preservatives, fragrances) or non-pharmaceutical endocrine-disrupting compounds (eg phthalates, polychlorinated biphenyls) in municipal wastewater.
- The health risks associated with antimicrobial resistance. Pharmaceutical residues (especially antibiotics and antimicrobial personal care products) in wastewater are a significant concern for their potential to accelerate the spread of antimicrobial resistance genes in the environment (Frascaroli et al. 2021); however, this is a rapidly growing field of research in its own right, and only risks associated with direct toxicological effects of pharmaceuticals will be considered here.
- Cytotoxic or antineoplastic pharmaceuticals will not be included, as these are covered by Eaton and Coxon (2023).

2. PHARMACEUTICAL USE IN NEW ZEALAND

Human pharmaceuticals are an essential part of healthcare in New Zealand, being used extensively in both community and hospital care settings (Ministry of Health 2007). They can be grouped according to three main types: prescription pharmaceuticals dispensed to individuals through a community pharmacy; pharmaceuticals dispensed and administered to individuals in the hospital; and over-the-counter pharmaceuticals that can be obtained without prescription (although these may also be available with a prescription). Over-the-counter pharmaceuticals can themselves be grouped according to three types: general sales medications that are freely available from pharmacies and other retail outlets such as supermarkets; pharmacy-only medications available only at pharmacies; and pharmacist-only medications that are available only at pharmacies following consultation with a pharmacist.[3]

The New Zealand Government, through the Pharmaceutical Management Agency (commonly known as Pharmac), currently fund the availability of over 1,300 different 'chemicals' (as >3,300 preparations) as medicines in hospitals and pharmacies. Over 50 million prescriptions for funded medications are dispensed from community pharmacies each year, with many further medications purchased over the counter without prescription.[4] For the purposes of this report, the focus will be prescription and over-the-counter pharmaceuticals that are used in the community, having been dispensed by a community pharmacy. Pharmaceuticals used in a hospital setting may differ from those used in the community, reflecting their use in patients with more serious illness and/or use in services such as surgery; for example, there will be greater use of restricted drugs such as anaesthetics and opioid analgesics than are used in general community settings, or higher doses of specific antibiotics. The presence of pharmaceuticals in hospital wastewaters is considered as part of a wider group of hazardous contaminants in a separate report (Jordan and Eaton 2024).

Many pharmaceuticals can be used to treat a number of different health conditions, therefore the therapeutic classes assigned to an API here should be considered indicative or in line with the primary use or mode of action, rather than being exclusive. For example, carbamazepine is used to prevent seizures caused by epilepsy and is therefore commonly considered to be an anticonvulsant, however it is also routinely used to control some mood disorders such as bipolar disorder and depression.[5] Similarly, the opioid analgesic hydrocodone is primarily used in pain management but also prescribed as an antitussive (cough suppressant), ranitidine and cimetidine are a type of antihistamine that is used to treat gastric acid reflux and prevent peptic ulcers, and diuretics are used to relieve hypertension.

[3] https://www.medsafe.govt.nz/projects/b5/otcinfo4consumersmarch2013.asp
[4] https://www.psnz.org.nz/careers/pharmacy
[5] https://healthify.nz/medicines-a-z/c/carbamazepine/

2.1 PHARMACEUTICAL USE IN NEW ZEALAND

2.1.1 Prescription pharmaceuticals

Data on the dispensing of prescription medications by community pharmacies in Aotearoa New Zealand was obtained from the Health NZ Pharmaceutical Web tool (Health NZ 2023). Data extracted for 1 January to 31 December 2022 includes entries for 780 different 'chemicals.'[6] A list of the top 100 pharmaceuticals prescribed in New Zealand, as determined by the number of dispensings, is presented in Table 1. The Web Tool is based on data held within the Pharmaceutical Collection, a data warehouse jointly owned by Pharmac and the Ministry of Health that records claims submitted by pharmacies for the reimbursement of subsidised medications that have been dispensed to patients (Raghunadan et al. 2021). It includes data on dispensings to individuals by a community pharmacy that are subsidised by the New Zealand Government; it does not include privately-funded medications (eg an unsubsidised medication or where a patient is ineligible for subsidy), medications purchased OTC (even if that medication is available and funded by prescription, for example, paracetamol), bulk practitioner supply orders, or pharmaceuticals administered in hospitals, and excludes some specific treatments such as cancer therapies (Health NZ 2023).

It should be noted that dispensing events alone will not provide a complete representation of the overall usage of different prescription pharmaceuticals in the community, because not all pharmaceuticals are dispensed in the same way. For example, paracetamol, in addition to being available as an OTC medication, is also commonly dispensed as a relatively large number of doses at a time (eg, in packs containing 100 x 500 mg tablets[7]); in 2022, there were 4,674,815 dispensings of paracetamol across all doses and formulations to 1,717,581 individuals – an average of 2.7 dispensing events per person over the year (Health NZ 2023). In contrast, medications like methadone appear high on the list of medications dispensed, because they are dispensed in a small number of doses each time – often a single or several doses, which may be administered under pharmacist supervision.[8] Although there was a total of 1,620,976 dispensings of methadone in 2022, these were to 6,967 individuals – average of 232 dispensings per person (Health NZ 2023). Nonetheless, dispensing data does provide a useful screening and prioritisation mechanism, to inform the pharmaceuticals we may expect to see in wastewater in New Zealand.

Among those most commonly prescribed are analgesics such as paracetamol (also known as acetaminophen), codeine and tramadol; NSAIDs including aspirin, ibuprofen and celecoxib; drugs for managing various psychiatric conditions including quetiapine, amitriptyline and fluoxetine; beta blockers and other anti-hypertensives including metoprolol, cilazapril, losartan and felodipine; the lipid regulators atorvastatin and simvastatin; antihistamines such as cetirizine and loratadine; omeprazole and pantoprazole, used in managing gastric reflux and ulcers; anti-asthmatic medications such as salbutamol, fluticasone and budesonide; diuretics including furosemide; hormones including levothyroxine and osetradiol; and antibiotics including amoxicillin.

[6] Within the Web Tool, different medications and therapeutic products are identified as 'chemicals.' Although these are predominantly pharmaceutical compounds, a small number of non-chemical items that are government-funded when obtained through prescription are also included, such as gluten-free flour and bread mixes, and insulin pumps, cartridges and needles.

[7] https://www.medsafe.govt.nz/profs/class/Minutes/2021-2025/71mccMin14Nov2023Paracetamol.pdf

[8] https://www.health.govt.nz/system/files/documents/publications/nz-practice-guidelines-opioid-substitution-treatment-apr14-v2.pdf

Table 1: Top 100 pharmaceuticals prescribed in New Zealand from 2020-2022, as determined by the number of total dispensings (initial and repeat dispensings).

Pharmaceutical compound	Therapeutic group	Total number of dispensings		
		2022	2021	2020
Paracetamol (Acetaminophen)	Analgesic/NSAIDs	4,674,815	4,080,771	3,743,371
Atorvastatin	Lipid regulators and statins	2,943,483	2,774,504	3,085,739
Omeprazole	PPI/anti-ulcers	2,673,484	2,835,339	2,831,991
Aspirin	Analgesics/NSAIDs	1,901,350	1,925,749	2,266,854
Metoprolol succinate	Beta blockers	1,664,598	1,685,734	1,958,394
Colecalciferol	Vitamins/supplements	1,635,060	1,539,962	1,612,620
Methadone hydrochloride	Opioid analgesics	1,620,976	1,682,073	1,728,719
Salbutamol	Anti-asthmatics	1,344,320	1,224,154	1,331,395
Ibuprofen	Analgesics/NSAIDs	1,281,339	1,062,661	1,030,298
Zopiclone	Sleeping pill	1,226,194	1,192,365	1,159,564
Cilazapril	Anti-hypertensive	1,212,194	1,578,443	1,686,982
Levothyroxine	Hormones	1,094,379	1,070,052	1,252,100
Amoxicillin	Antibiotic	1,084,748	888,887	805,660
Quetiapine	Psychiatric drugs	1,057,853	1,019,809	941,920
Metformin hydrochloride	Anti-diabetic	1,032,389	1,044,350	1,259,244
Furosemide	Diuretic	1,012,342	89,2721	931,183
Losartan potassium	Anti-hypertensive	1,012,016	562,455	556,703
Amlodipine	Anti-hypertensive	1,002,662	1,180,614	1,143,761
Docusate sodium with sennosides	Laxative	984,614	976,304	938,903
Fluticasone propionate	Anti-asthmatic	935,831	879,831	872,992
Quinapril	Anti-hypertensive	934,495	712,375	637,812
Budesonide with eformoterol	Anti-asthmatic	904,142	713,911	566,034
Candesartan cilexetil	Anti-hypertensive	875,849	705,547	716,174
Allopurinol	Gout medication	870,824	843,507	926,427
Cetirizine hydrochloride	Antihistamine	822,850	738,538	803,001
Prednisone	Corticosteroid	797,649	731,379	745,292
Celecoxib	Analgesics/NSAIDs	797,174	712,596	605,250
Amitriptyline	Psychiatric drugs	792,055	788,712	758,891
Felodipine	Anti-hypertensive	770,375	762,658	909,750
Codeine phosphate	Analgesics/NSAIDs	736,963	731,352	704,471
Tramadol hydrochloride	Analgesics/NSAIDs	729,185	722,086	692,094
Fluoxetine hydrochloride	Psychiatric drugs	703,574	707,055	654,734
Loratadine	Antihistamine	702,641	661,549	735,524
Dabigatran	Anti-thrombotics	668,387	650,926	628,932
Sertraline	Psychiatric	628,219	646,714	558,933
Doxazosin	Anti-hypertensive	618,213	594,739	590,788
Blood glucose diagnostic test strip	Anti-diabetic	589,620	597,903	593,596
Venlafaxine	Psychiatric drugs	576,056	557,554	574,003
Simvastatin	Lipid regulators and statins	558,005	609,456	786,298
Citalopram hydrobromide	Psychiatric drugs	548,444	576,691	677,834
Amoxicillin with clavulanic acid	Antibiotics	527,512	525,046	519,692
Bisoprolol fumarate	Beta blocker	524,547	447,792	421,818

Table 1 continued. Top 100 pharmaceuticals prescribed in New Zealand from 2020-2022, as determined by the number of total dispensings (initial and repeat dispensings).

Pharmaceutical compound	Therapeutic group	Total number of dispensings		
		2022	2021	2020
Vildagliptin with metformin hydrochloride	Anti-diabetic	510,251	464,258	286,881
Nortriptyline hydrochloride	Psychiatric drugs	499,420	488,165	471,231
Rivaroxaban	Anti-thrombotics	488,119	388,057	270,341
Buprenorphine with naloxone	Opioid analgesics	485,558	492,169	452,332
Escitalopram	Psychiatric	469,755	455,835	478,838
Morphine sulphate	Opioid analgesics	469,480	481,415	469,663
Pantoprazole	PPI/anti-ulcers	467,418	457,442	499,764
Cetomacrogol with glycerol	Emollient	462,390	389,878	401,595
Insulin glargine	Anti-diabetic	452,989	449,803	429,578
Folic acid	Vitamins/supplements	447,190	400,506	426,602
Pregabalin	Anti-convulsant	434,901	340,633	260,779
Fluticasone with salmeterol	Anti-asthmatic	433,740	455,970	528,797
Gabapentin	Anti-convulsant	428,869	425,061	434,061
Paracetamol with codeine	Analgesic/NSAIDs	427,394	399,512	394,374
Diclofenac sodium	Analgesic/NSAIDs	422,566	423,052	453,477
Olanzapine	Psychiatric drugs	416,542	400,846	376,858
Flucloxacillin	Antibiotics	412,048	420,674	433,386
Lorazepam	Psychiatric drugs	407,257	387,548	360,590
Oxycodone hydrochloride	Opioid analgesic	403,824	395,161	366,620
Mirtazapine	Psychiatric drugs	398,644	365,780	317,404
Diltiazem hydrochloride	Anti-hypertensive	392,146	360,394	424,415
Diazepam	Psychiatric drugs	385,561	396,341	393,821
Fluticasone furoate with vilanterol	Anti-asthmatic	371,881	351,426	330,031
Sodium valproate	Anti-convulsant	366,796	376,527	372,929
Perindopril	Anti-hypertensive	366,046	213,895	849,27
Vitamins	Vitamins/supplements	360,067	346,275	370,973
Bendroflumethiazide	Diuretic	345,525	341,617	428,813
Losartan potassium with hydrochlorothiazide	Anti-hypertensive	345,461	262,304	228,76
Clopidogrel	Anti-thrombotics	344,152	331,053	353,524
Clonazepam	Psychiatric drugs	322,155	328,603	319,525
Fluticasone	Corticosteroid	307,414	297,580	361,809
Empagliflozin	Anti-diabetic	306,086	179,207	N//A
Oestradiol	Hormones	299,826	206,119	125,497
Ondansetron	Antiemetics	291,413	239,932	221,574
Cefalexin	Antibiotics	287,723	263,934	218,141
Vildagliptin	Anti-diabetics	286,197	254,829	188,329
Doxycycline	Antibiotics	281,159	253,398	281,739
Hydrocortisone butyrate	Corticosteroid	271,022	295,890	311,337
Risperidone	Psychiatric drugs	267,276	263,656	258,318
Lactulose	Laxative	264,791	273,214	281,190

Table 1 continued. Top 100 pharmaceuticals prescribed in New Zealand from 2020-2022, as determined by the number of total dispensings (initial and repeat dispensings).

Pharmaceutical compound	Therapeutic group	Total number of dispensings		
		2022	2021	2020
Spironolactone	Diuretic	264,306	245,912	252,089
Nicotine	Stimulant	263,894	275,737	276,055
Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride	Laxative	257,191	225,464	189,661
Methylphenidate hydrochloride	Psychiatric drug	248,751	213,801	188,630
Influenza vaccine	Vaccine	247,214	123,511	140,212
Solifenacin succinate		242,895	214,601	187,211
Gliclazide	Anti-diabetic	241,678	276,376	334,246
Hydrocortisone	Corticosteroid	237,358	234,260	249,684
Hydrocortisone with miconazole	Corticosteroid/antifungal	233,673	228,985	224,297
Chloramphenicol	Antibiotics	229,970	209,867	198,548
Methylphenidate hydrochloride extended-release	Psychiatric drugs	229,336	190,697	155,940
Naproxen	Analgesics/NSAIDs	223,623	228,905	236,522
Orphenadrine citrate	Muscle relaxant	223,595	219,116	191,999
Oestriol	Hormones	218,792	201,270	197,729
Chlortalidone	Diuretic	217,142	192,878	119,774
Ferrous sulfate	Vitamins/supplements	217,058	205,732	232,549
Budesonide	Corticosteroids	213,910	168,881	160,537
Isosorbide mononitrate	Nitrates; anti-hypertensive	210,611	211,720	230,481

The data here is generally consistent with data available from Pharmac, describing the 100 most widely-prescribed pharmaceuticals for the 2018-19 financial year, and the top 20 medications for each year since then (see Appendix A). Note that some data from 2020 was skewed by changes in dispensing patterns during the COVID-19 pandemic; further information is available in the Web Tool.

2.1.2 Over-the-counter therapies

Accurate data on OTC therapies is difficult to obtain since few, if any, records are kept of their sale or are commercially sensitive (Peake et al. 2016). According to market research and data company Statista[9], the OTC pharmaceuticals[10] market in New Zealand is projected to generate a revenue of USD$429 million in 2024, and is dominated by analgesics, cough and cold remedies, vitamins and minerals, and 'other OTCs.' This is consistent with general trends of OTC pharmaceutical usage highlighted by Peake et al. (2016).

Some common examples of APIs present in OTC therapies are included in Table 2. The most widely-used OTC analgesics and NSAIDs include paracetamol, aspirin, ibuprofen, diclofenac and codeine,[11] all of which are also represented in the list of highly-prescribed pharmaceuticals. Over-the-counter cough and cold medications and remedies can contain a variety of APIs to treat specific symptoms, including various expectorants, decongestants, antitussives and antihistamines, and may also contain paracetamol as pain relief and/or antipyretic. Antihistamines are also commonly used in the relief of hayfever and allergies, with some also used as sleep aids (ie, sedating or drowsy antihistamines) or to prevent nausea and motion sickness[12]. Vitamin and mineral supplements are not usually considered to be medications or pharmaceuticals, although they may be prescribed for therapeutic use and assume the role of a 'medicine' in certain doses (eg, folic acid or iron) (Peake et al. 2016). As the primary source of most vitamins and supplements is likely to be dietary exposure rather than therapeutic use, they will not be considered further within this report. Similarly, caffeine and nicotine may be used in a therapeutic context, but are more commonly consumed as lifestyle substances (eg in coffee or through smoking or vaping) and will not be considered further.

[9] https://www.statista.com/outlook/hmo/otc-pharmaceuticals/new-zealand
[10] This data set includes natural and synthetic agents, analgesics, cough and cold remedies, vitamins and minerals, digestive and intestinal remedies, hand sanitisers, eye care, sleep aids, wound care, skin treatments and 'other OTCs,' and excludes homeopathic remedies.
[11] Codeine is only available OTC when the formulation includes other active ingredients such as paracetamol; codeine as a single active ingredient must be prescribed.
[12] https://healthify.nz/medicines-a-z/a/antihistamines/

Table 2: Examples of APIs found in common OTC therapies

Therapeutic group	Expected function	Examples
Analgesics and NSAIDs	Relieve pain, inflammation and/or fever	Paracetamol Ibuprofen Diclofenac Aspirin Codeine
Cold and flu remedies[a]	Expectorants and mucolytics help loosen phlegm from the respiratory tract, making it easier to expel	Bromhexine Guaifenesin Ipecacuanha
	Antitussives reduce coughing	Dextromethorphan Pholcodine
	Decongestants reduce blocked and/or runny noses	Oxymetazoline Phenylephrine Pseudoephedrine Xylometazoline
	Antibacterials and antiseptics used in lozenges and spays to treat sore throats	Amylmetacresol Benzydamine hydrochloride Cetylpyridinium chloride Dichlorobenzyl alcohol Lidocaine hydrochloride
Antihistamines	Relief from symptoms allergic rhinitis and hay fever (runny nose, sneezing, itchy or watery eyes). May also be combined with other APIs for use in cold and flu remedies.	Brompheniramine Chlorphenamine Diphenhydramine Doxylamine Levocetirizine Promethazine Triprolidine
Sleep aids	Help bring about sleep or maintain a state of sleep	Diphenhydramine Doxylamine Melatonin

[a] https://medsafe.govt.nz/hot/alerts/CoughandCold/InfoOct2009.asp

3. PRESENCE OF PHARMACEUTICALS IN NEW ZEALAND WASTEWATER

Relatively few assessments of pharmaceuticals in wastewater (and indeed, of emerging organic contaminants as a group) have been conducted in New Zealand (Tremblay and Northcott 2015; Bernot et al. 2019). Monitoring of chemical contaminants has focused largely on traditional contaminants such as trace metals, nutrients, hydrocarbons, and legacy pesticides, for which there are extensive guidelines and management practices prescribed (MacDonald and Conwell 2021). In contrast, most EOCs, including pharmaceuticals, are not commonly monitored in wastewater or the environment, so their presence and potential impacts on environmental and/or human health are poorly characterised (Tremblay and Northcott 2015; PCE 2022). Further, most of the New Zealand data is relatively ad-hoc, being collected in discrete studies that focus on a small number of contaminants from a single WWTP or a small geographic area, and there are differences in sample collection, analytical methods, data analysis and/or reporting that complicate data collation and synthesis, and therefore make it difficult to understand the current state of knowledge and key knowledge gaps (MacDonald and Conwell 2021; PCE 2022). Indeed, in preparing this report, we found that the data on pharmaceutical concentrations in wastewaters was very limited, and often difficult to locate: only a small amount of the data had been published in the scientific literature (Sarmah et al. 2006; Gielen et al. 2009; Kumar et al. 2019; Moreau et al. 2019; Emnet et al. 2020), with the rest published in technical reports prepared on behalf of local councils or WWTP operators (often as part of the environmental impact assessments or related processes required during Resource Consent applications or renewals), or from post-graduate research/theses. Moreover, not all of the studies or analyses that have been carried out to date were available or accessible for inclusion in the current review, either because they do not appear to have been publicly released or because the work has yet to be completed. For example, we found several instances in which seemingly key studies were referenced by other reports, but could not be located (eg, Northcott et al. (2013), Northcott (2017, 2019)). Similarly, in their recent technical report, Campos et al. (2023) note that between 2013 and 2023, a database of EOCs measured in samples of treated wastewater from New Zealand wastewater treatment plants was collated, containing data from 25 samples collected across 11 WWTPs representing a broad range of catchment populations, influent volumes, relative domestic and industrial inputs, treatment processes and geographic distribution (Northcott, unpublished data, as cited in Campos et al. 2023). Unfortunately, neither the database nor many of the studies/samples included in it were accessible at the time of preparing this report. As such, although we had intended that our reporting on the presence of pharmaceuticals would be prioritised on the basis of prescribing and dispensing data, we report here all of the data which we were able to locate within the timeframe available.

3.1 COMMENT ON METHODOLOGY

It is important to bear in mind that data on the concentrations of pharmaceuticals in wastewater usually reflects the dissolved fraction only. Because of the amount of suspended solids and organic content in wastewater, sample preparation requires a filtration step, with the filtrate subsequently concentrated and analysed using a combination of techniques such as solid-phase extraction (SPE) and high performance liquid chromatography with mass spectrometry (HPLC-MS), and the filtered material discarded (Gielen 2007; Peake et al. 2016). However, many contaminants in wastewater, including some pharmaceuticals, can adsorb to solids and will therefore not be accounted for if the particulate phase is not also analysed, leading to the possible underestimation of the true contaminant load (Gielen 2007; Tremblay and Northcott 2015). This is not unique to New Zealand studies, but is consistent with methods used internationally, thus comparisons between New Zealand and international data sets remain valid. Further, the extent to which compounds adsorb to particulates or colloids is a function of the physiochemical characteristics of the compound, so that any underestimation of load will be biased towards certain types of compounds; as many (but not all) pharmaceuticals show relatively low levels of adsorption, this is likely to be a minor issue in determining their load. Finally, whilst analysing the dissolved fraction alone likely underestimates the load of pharmaceuticals in raw wastewaters that may be discharged to the environment in situations such as overflows, spills or leaks, such data is still likely to be an accurate reflection of the pharmaceutical load in final effluents that have undergone settling, clarification and related treatment process, where most of the particulate fraction has been removed. Data obtained from analysing dissolved fractions will also be less informative in understanding the potential pharmaceutical load of sludges or biosolids.

3.2 PRESENCE OF PHARMACEUTICALS IN AOTEAROA NEW ZEALAND WASTEWATER

Factors influencing the composition of municipal wastewater, including the presence and concentration of pharmaceuticals, include population characteristics (eg, population size, density, demographics and general health status), land use within the catchment (eg, residential, commercial, agricultural, industrial), the presence of certain facilities or types of industry (eg, large hospitals, pharmaceutical research or manufacturing facilities) and national health regulations and habits (eg, MedSafe approval, public funding, population attitudes towards medications, treatment compliance) (Gielen 2007).

As discussed above, relatively few studies have assessed the presence of pharmaceuticals in New Zealand wastewater, and not all of these were available for inclusion in this review. Data obtained in these studies are summarised in Table 3 (for untreated wastewater and primary screened influents) and Table 4 (for treated wastewater effluents). Much of the data focuses on a small number of compounds, with those most commonly assayed and detected including the highly-consumed analgesics acetaminophen (paracetamol), ibuprofen and naproxen, as well as the anti-epileptic carbamazepine, which is also commonly prescribed as an antidepressant.

3.2.1 Untreated/influent wastewaters

Kumar et al. (2019) analysed influent and effluent from a WWTP receiving domestic wastewater (approximately 100,000 people) with small contributions of dairy, meat processing and waste management effluents. The treatment plant comprised primary and secondary (parallel 5-stage Bardenpho and membrane bioreactor) treatments. They assessed the seasonal presence of 12 different pharmaceuticals and several other target EOCs, all of which were detected, often with a detection rate of 97 to 100%. Total PPCP load in influent was highest in winter (average 183 µg/L), presumably due to increased consumption of medications relating to winter-prevalent illness (eg, cold and flu medications, analgesics, antibiotics), and lowest in spring (89 µg/L). Total PPCP load in effluent was greatly reduced compared to influents and similar for all seasons, averaging 6,364 ng/L. For influents, the pharmaceuticals with the highest concentrations were analgesics (acetaminophen, ibuprofen, naproxen) and beta blockers (metoprolol), while metoprolol was dominant in effluents. The concentrations of some compounds exhibited seasonal variation, for example NSAIDs and antibiotics were present at highest concentrations over winter.

Tong (2013) analysed the presence of pharmaceuticals in influent and effluent from a single round of sampling from an undisclosed WWTP employing secondary treatment. Target pharmaceuticals included bezafibrate, carbamazepine, diclofenac sodium, fluoxetine hydrochloride, furosemide, ibuprofen, metoprolol, paracetamol, salicylic acid, sulfamethoxazole, trimethoprim and venlafaxine. Seven of these - carbamazepine, fluoxetine, metoprolol, paracetamol, sulfamethoxazole, trimethoprim, bezafibrate – were detected in both influent and effluent, while the remaining compounds were detected in neither influent nor effluent. Their methods focused on detection only, rather than quantification.

Northcott (2017) (as cited in Stewart 2020) assessed the presence of 81 EOCs (including 10 pharmaceuticals and 16 steroid hormones) in both the dissolved and particulate phases of untreated wastewater from Gisborne WWTP. Among the target pharmaceuticals and steroid hormones, they detected the NSAIDs diclofenac, ibuprofen and naproxen in the low µg/L range (up to a maximum of nearly 17 µg/L for ibuprofen), with ketoprofen and meclofenamic acid, together with carbamazepine, in the tens to several hundred ng/L range. The synthetic hormones 17α-ethinyl estradiol and mestranol were present at significantly lower concentrations, in the several ng/L range. Stewart (2020) subsequently assessed the potential risk to ecological health posed by sewage overflow events, and determined that although a number of EOCs exhibited potential ecological risk at the levels observed in untreated wastewater, dilution by receiving environments significantly reduced the risk, which could be considered to be low. Human exposure was not determined due to lack of analytical methods for these compounds in shellfish (which could become contaminated prior to harvesting and consumption), and the lack of potential exposure via drinking water given nature of the marine receiving environment.

Analysis of influent and treated wastewater from the Porirua WWTP that utilises preliminary screening, secondary treatment by activated sludge and tertiary UV treatment (Northcott (2019, as cited in Peterson and Cameron (2020) and Cameron et al. (2023)) determined that the profile and concentration of EOCs was similar to that seen for influent and effluent at other WWTPs in New Zealand. Among the pharmaceuticals detected were carbamazepine, diclofenac, ibuprofen and naproxen, as well as the steroid hormones estrone and 17β-estradiol.

Chappell et al. (2022) analysed untreated wastewaters collected from 37 WWTP around the country for illicit substances. Methamphetamine, cocaine and MDMA were detected at various locations, but no samples contained detectable levels of fentanyl or heroin.

3.2.2 Treated/effluent wastewaters

Sarmah et al. (2006) determined the presence of estrogens in effluents from three WWTP in the Waikato region. In addition to natural estrogens estrone (E1), 17β-estradiol (E2), and estriol (E3), all of which are also used in prescription medications, they detected trace levels of the synthetic estrogen 17α-ethinyl estradiol (EE2) in the effluent from one plant. Similarly, van der Korght (2008) analysed effluent from three small WWTP for natural and synthetic hormones, detecting E3 but not EE2 or several other natural hormones.

Gielen (2007) assessed the presence of 12 commonly-used pharmaceuticals from different therapeutic classes in effluent from the Rotorua WWTP, which serves approximately 70,000 people and utilises preliminary screening and grit settling, primary clarifiers and a 5-stage Bardenpho process with activated sludge for nutrient removal. They noted that the pharmaceuticals selected differed in their chemical nature, making it difficult to optimise conditions for the extraction and analysis of all compounds of interest. Naproxen and carbamazepine were present at the highest concentrations (just under 1 mg/L), with ibuprofen, amitriptyline, 17α-ethinylestradiol, diltiazem and salicylic acid also detected.

Stewart (2016) collected composite effluent samples from the Omaha WWTP in Auckland. Although they included only a small number of pharmaceuticals within a larger EOC suite, they detected ibuprofen, diclofenac and acetaminophen, though not 17α-ethinyl estradiol, and determined that concentrations of EOCs in the effluent were generally low compared with the published literature (eg Luo et al. 2014; Margot et al. 2015).

Northcott and Tremblay (2017) analysed effluents from the Bell Island WWTP in Nelson for 80 EOCs, with 23 compounds detected, including six acidic pharmaceuticals (acetaminophen, carbamazepine, diclofenac, ibuprofen, naproxen and salicylic acid). Comparison of the wider suite of EOCs determined that they were within range of, or lower than, those measured at other WWTPs around New Zealand during a national survey (Northcott et al. (2013), as cited in Northcott and Tremblay (2017)), and that they were considerably lower than those considered to present a risk to aquatic organisms or to human health. The authors also note, however, the lack of information available to properly characterise the effects of environmental exposure to EOCs on ecological and/or human health, and highlight the importance of remaining up-to-date as the science and understanding in this space progresses.

Emnet et al. (2020) collected WWTP effluents from three small communities around Whakaraupō/Lyttleton Harbour, and analysed them for various EOCs. Pharmaceutical assays were restricted to hormones, where they detected the natural hormones E1 in all three WWTP, and E2 and E3 at two WWTP, with the synthetic estrogen EE2 detected in one sample from one site.

Campos et al. (2023) collected and analysed two samples of treated wastewater from the Nelson North WWTP, with one sample each collected during wet and dry weather. Forty-five of 84 target EOC analytes were detected, including 7 pharmaceuticals (acetaminophen,

carbamazepine, diclofenac, ibuprofen, ketoprofen, naproxen, salicylic acid). Overall, concentrations of EOCs were generally higher at this WWTP than at other WWTPs around New Zealand, suggesting that removal of EOCs at Nelson North WWTP was less efficient than other plants; however, the lack of analysis of influent samples or particulate phase analysis meant it was not possible to exclude higher influent EOC load or different phase partitioning as contributing factors.

Moreau et al. (2019) analysed effluent from an undisclosed WWTP to complement their survey of EOCs in groundwater across the Waikato. In screening for 315 pharmaceuticals or drugs of abuse, they detected 39 compounds: metformin was present in extremely high concentrations (200 mg/L), with gabapentin, 10,11-dihydroxycarbamazepine (a carbamazepine metabolite), levamisole, sotalol, atenolol, celiprolol, morphine, sulfamethoxazole, tramadol, venlafaxine, carbamazepine, diclofenac and ibuprofen all detected in the several mg/L range.

Although vastly different in scale and design to a municipal wastewater network, the principle of onsite wastewater management systems in receiving and treating domestic wastewater is essentially similar. Sampling from onsite wastewater management systems (ie, ‘septic tanks’) in Canterbury detected acetaminophen, carbamazepine, ibuprofen, naproxen and trimethoprim, mostly in the tens of ng/L range, although ibuprofen was present at low µg/L range (Humphries et al. 2024).

Table 3: Concentrations and detection rates (as percentage of samples) of pharmaceuticals detected in untreated/influent wastewater from New Zealand studies.

Therapeutic group	Pharmaceutical compound	%	Concentration (ng/L)			Reference
			Mean	Median	Maximum	
Analgesic/ NSAIDs	Acetaminophen	100	49,037	30,669		Kumar et al. (2019)
			detected [c]			Tong (2013)
	Diclofenac	100	183	172		Kumar et al. (2019)
			ND			Tong (2013)
			1,071 [a]		1,157 [a]	Stewart (2020)
				502	556	Cameron et al. (2023)
	Ibuprofen	100	7,552	7,947		Kumar et al. (2019)
			1,156 [b]			Gielen (2007)
			ND			Tong (2013)
			12,677 [a]		16,882 [a]	Stewart (2020)
				7,146	9,323	Cameron et al. (2023)
	Ketoprofen		123 [a]		168 [a]	Stewart (2020)
	Meclofenamic acid		15.7 [a]		18.5 [a]	Stewart (2020)
	Naproxen	97	4,563	4,930		Kumar et al. (2019)
			5,042 [b]			Gielen (2007)
			8,908 [a]		11,824 [a]	Stewart (2020)
				2,620	2,953	Cameron et al. (2023)
	Salicylic acid		704 [b]			Gielen (2007)
			ND			Tong (2013)
				515	1,151	Cameron et al. (2023)
Antibiotics	Clarithromycin	54	27	15		Kumar et al. (2019)
	Roxithromycin	97	22	25		Kumar et al. (2019)
	Sulfamethoxazole	97	713	627		Kumar et al. (2019)
			detected [c]			Tong (2013)
	Trimethoprim	100	590	571		Kumar et al. (2019)
			detected [c]			Tong (2013)
Anti-convulsants	Carbamazepine	100	589	599		Kumar et al. (2019)
			301 [b]			Gielen (2007)
			detected [c]			Tong (2013)
			666 [a]		794 [a]	Stewart (2020)
				684	846	Cameron et al (2023)
Anti-diabetics	Metformin	100	detected [d]	detected [d]		Kumar et al. (2019)
Anti-hypertensives	Diltiazem		69 [b]			Gielen (2007)
Beta blockers	Atenolol	100	763	456		Kumar et al. (2019)
	Metoprolol	100	5,242	5,444		Kumar et al. (2019)
			detected [c]			Tong (2013)
Blood lipid regulators	Bezafibrate		detected [c]			Tong (2013)
Diuretics	Furosemide		ND			Tong (2013)
Opioids and illicit substances	Cocaine		detected [c]			Chappell et al. (2022)
	Fentanyl		detected [d]			Chappell et al. (2022)
	Heroin		ND			Chappell et al. (2022)
	MDMA		detected [c]			Chappell et al. (2022)
	Methamphetamine		detected [c]			Chappell et al. (2022)

Table 3 continued. Concentrations and detection rates (as percentage) of pharmaceuticals detected in untreated/influent wastewater from New Zealand studies.

Therapeutic group	Pharmaceutical compound	%	Concentration (ng/L)			Reference
			Mean	Median	Maximum	
Psychiatric drugs	Fluoxetine	100	50	50		Kumar et al. (2019)
			detected [c]			Tong (2013)
	Venlafaxine		ND			Tong (2013)
Steroid hormones	Estrone (E1)		51 [a]		135 [a]	Stewart (2020)
				79	83	Cameron et al. (2023)
	17β-estradiol (E2)			28.3	34.5	Cameron et al. (2023)
	17α-ethinyl estradiol (EE2)		24 [b]			Gielen (2007)
			5.5 [a]		8.6 [a]	Stewart (2020)
	Mestranol		4.3 [a]		7.7 [a]	Stewart (2020)

ND – not detected

[a] total concentration for both particulate and dissolved fractions.

[b] estimated from concentration in final effluents and a 50/50 mixture of final effluents and raw influent.

[c] assay was presence/absence only; no attempt was made to quantify analytes.

[d] detected but not quantified for some other reason (eg, less than the limit of quantitation (<LOQ) or less than the limit of reporting (<LOR), matrix interference)

Table 4: Concentrations and detection rates (as percentage) of pharmaceuticals detected in treated wastewater effluents from New Zealand studies.

Therapeutic group	Pharmaceutical compound	%	Concentration (ng/L)			Reference
			Mean[a]	Median	Maximum	
Analgesic/ NSAIDs	Acetaminophen	75	detected [d]	detected [d]	detected [d]	Kumar et al. (2019)
			ND			Gielen (2007)
			detected [c]			Tong (2013)
			9.1*			Northcott and Tremblay (2017)
		100	82,096		86,184	Campos et al. (2023)
			ND			Moreau et al. (2019)
			82 [b]			Humphries et al. (2024)
		100	6±0			Stewart (2016)
	Aspirin		detected [d]			Moreau et al. (2019)
			detected[b ,d]			Humphries et al. (2024)
	Codeine		2,600			Moreau et al. (2019)
	Diclofenac	100	303	250	561	Kumar et al. (2019)
			ND			Tong (2013)
			19.4 [b]			Northcott and Tremblay (2017)
		100	316		397	Campos et al. (2023)
			detected [d] [b]			Humphries et al. (2024)
			1,000			Moreau et al. (2019)
					913	Peterson and Cameron (2020)
		100	51±7			Stewart (2016)
	Ibuprofen	100	detected [d]	detected [d]	detected [d]	Kumar et al. (2019)
			41±13			Gielen (2007)
			168 [b]			Gielen (2007)
			ND			Tong (2013)
			6.1[b]			Northcott and Tremblay (2017)
		100	8,722		10,173	Campos et al. (2023)
			1,000			Moreau et al. (2019)
			2,018[b]			Humphries et al. (2024)
		100	145±7			Stewart (2016)
					62	Peterson and Cameron (2020)
	Ketoprofen	100	50.9		63.7	Campos et al. (2023)
			ND[b]			Humphries et al. (2024)
	Lidocaine		ND[b]			Humphries et al. (2024)
	Meclofenamic acid		ND[b]			Humphries et al. (2024)
	Naproxen	100	detected [d]	detected [d]	detected [d]	Kumar et al. (2019)
			987±208			Gielen (2007)
			1,202[b]			Gielen (2007)
			158[b]			Northcott and Tremblay (2017)
		100	2,187		2,831	Campos et al. (2023)
			13.6[b]			Humphries et al. (2024)
					182	Peterson and Cameron (2020)

Table 4 continued. Concentrations and detection rates (as percentage) of pharmaceuticals detected in treated wastewater effluents from New Zealand studies.

Therapeutic group	Pharmaceutical compound	%	Concentration (ng/L)			Reference
			Mean[a]	Median	Maximum	
Analgesic/ NSAIDs	Salicylic acid		<1			Gielen (2007)
			36[b]			Gielen (2007)
			ND			Tong (2013)
			44.4[b]			Northcott and Tremblay (2017)
		100	7,360		9,231	Campos et al. (2023)
					36.3	Peterson and Cameron (2020)
			ND[b]			Humphries et al. (2024)
	Tramadol		1,300			Moreau et al. (2019)
Antibiotics	Clarithromycin	50	1	1	4	Kumar et al. (2019)
	Roxithromycin	75	3	3	4	Kumar et al. (2019)
	Sulfamethoxazole	100	264	252	398	Kumar et al. (2019)
			detected [c]			Tong (2013)
			ND[b]			Humphries et al. (2024)
			1,700			Moreau et al. (2019)
	Trimethoprim	100	380	387	473	Kumar et al. (2019)
			detected [c]			Tong (2013)
			570			Moreau et al. (2019)
			0.4[b]			Humphries et al. (2024)
Anti-asthmatic	Salbutamol		330			Moreau et al. (2019)
Anti-convulsants	Carbamazepine	100	691	687	793	Kumar et al. (2019)
			709±33			Gielen (2007)
			407[b]			Gielen (2007)
			detected [c]			Tong (2013)
		100	315		347	Campos et al. (2023)
			302[b]			Northcott and Tremblay (2017)
			1,100			Moreau et al. (2019)
			120[b]			Humphries et al. (2024)
					536	Peterson and Cameron (2020)
	Gabapentin		26,000			Moreau et al. (2019)
	Lamotrigine		550			Moreau et al. (2019)
	Oxcarbazepine		490			Moreau et al. (2019)
	Phenobarbital		ND[b]			Humphries et al. (2024)
Anti-diabetics	Metformin	100	detected [d]	detected [d]	detected [d]	Kumar et al. (2019)
			200,000			Moreau et al. (2019)
Anti-hypertensives	Diltiazem		133±23			Gielen (2007)
			23[b]			Gielen (2007)
			370			Moreau et al. (2019)
	Felodipine		detected [d]			Moreau et al. (2019)
	Telmisartan		110			Moreau et al. (2019)
Anti-parasitics, anti-fungals, anti-helminthics	Levamisole		8,200			Moreau et al. (2019)
	Miconazole		13			Moreau et al. (2019)
	Oxfendazole		530			Moreau et al. (2019)
	Thiabendazole		24			Moreau et al. (2019)
Anti-thrombotics	Clopidogrel		28			Moreau et al. (2019)
	Warfarin		8			Moreau et al. (2019)

Table 4 continued. Concentrations and detection rates (as percentage) of pharmaceuticals detected in treated wastewater effluents from New Zealand studies.

Therapeutic group	Pharmaceutical compound	%	Concentration (ng/L)			Reference
			Mean[a]	Median	Maximum	
Beta blockers	Atenolol	100	237	125	611	Kumar et al. (2019)
			4,400			Moreau et al. (2019)
	Celiprolol		2,600			Moreau et al. (2019)
	Metoprolol	100	3,097	2,830	4,305	Kumar et al. (2019)
			detected [c]			Tong (2013)
	Sotalol		6,300			Moreau et al. (2019)
Blood lipid regulator and statins	Bezafibrate		detected [c]			Tong (2013)
	Clofibric acid		ND[b]			Humphries et al. (2024)
Diuretic	Furosemide		ND			Tong (2013)
			310			Moreau et al. (2019)
	Hydrochlorothiazide		600			Moreau et al. (2019)
Opioids and illicit substances	Dihydromorphine		570			Moreau et al. (2019)
	Ethylmorphine		160			Moreau et al. (2019)
	Morphine		2,000			Moreau et al. (2019)
	Normorphine		2,200			Moreau et al. (2019)
Psychiatric drugs	Amisulpride		610			Moreau et al. (2019)
	Amitriptyline		29.5±0.1			Gielen (2007)
			<1[b]			Gielen (2007)
	Chlorpromazine		<14			Gielen (2007)
			<14[b]			Gielen (2007)
	Fluoxetine	100	26	26	37	Kumar et al. (2019)
			detected [c]			Tong (2013)
	Oxazepam		97			Moreau et al. (2019)
	Thioridazine		<73			Gielen (2007)
			<73[b]			Gielen (2007)
	Venlafaxine		ND			Tong (2013)
			1,200			Moreau et al. (2019)
Steroid hormones	Estrone (E1)	100			84.7	Sarmah et al. (2006)
		82			113.8	Emnet et al. (2020)
					214	Peterson and Cameron (2020)
		100	20±2			Stewart (2016)
		50	1.75[b]		17.5	Campos et al. (2023)
	17α-estradiol	33			9.5	Sarmah et al. (2006)
		0			ND	van der Kroght (2018)
	17β-estradiol (E2)	100			14.8	Sarmah et al. (2006)
		0			ND	van der Kroght (2018)
		12			18.8	Emnet et al. (2020)
		0	<0.1			Stewart (2016)
					49.8	Peterson and Cameron (2020)
	Estriol (E3)	0			ND	Sarmah et al. (2006)
		67		31.9	58.3	van der Kroght (2018)
		3			13.1	Emnet et al. (2020)
		100	179		232	Campos et al. (2023)

Table 4 continued. Concentrations and detection rates (as percentage) of pharmaceuticals detected in treated wastewater effluents from New Zealand studies.

Therapeutic group	Pharmaceutical compound	%	Concentration (ng/L)			Reference
			Mean[a]	Median	Maximum	
Steroid hormones	17α-ethinyl estradiol (EE2)	33			trace	Sarmah et al. (2006)
		0			ND	van der Kroght (2018)
			8.6±3.6			Gielen (2007)
			4[b]			Gielen (2007)
		21			11.3	Emnet et al. (2020)
		0	<0.5			Stewart (2016)
Other	Flecainide		340			Moreau et al. (2019)
	Fexofenadine		500			Moreau et al. (2019)

ND – not detected.

[a] mean ± standard deviation, where these values were provided

[b] Denotes not a single value, rather than a true mean.

[c] assay was presence/absence only; no attempt was made to quantify analytes.

[d] detected but not quantified for some other reason (eg, <LOQ or LOR, matrix interference).

Note, Humphries et al. (2024) is effluent from a domestic OWMS rather than a municipal WWTP.

3.3 PRESENCE OF PHARMACEUTICALS IN NEW ZEALAND MUNICIPAL BIOSOLIDS AND WASTEWATER RECEIVING ENVIRONMENTS

Sewage sludge and biosolids are also well-documented internationally to contain a diverse array of pharmaceutical residues, with concentrations typically ranging from nanograms to micrograms per gram dry weight (Chen et al. 2013; Tran et al. 2018; Kinney and Vanden Huelvel 2020). Similarly, receiving environments for the discharge of wastewater effluents, or that are otherwise impacted by wastewater (eg, wastewater overflows or leaking septic tanks) are well known to contain pharmaceutical contaminants. The profile and concentrations of pharmaceutical residues present in sludges, biosolids and environmental samples tend to reflect patterns of use within the serviced community, as well as being influenced by treatment technologies and operating parameters within the WWTP and the physicochemical properties of individual compounds (Chen et al. 2013; Kinney and Vanden Huelvel 2020). Although outside the scope of this review, data on the presence of pharmaceuticals in sludge, biosolids or receiving/impacted environments can be useful to infer their presence in municipal wastewater (ie, as the source of those compounds to the sludge/biosolids/environment), and thus can be used to further build our understanding of their presence in New Zealand municipal wastewater, in the face of otherwise limited data. Notably, though not unexpectedly, there is also a dearth of information on pharmaceuticals in these matrices in New Zealand. A summary of the available data is provided below, with additional details in Appendix B.

The presence of pharmaceuticals in sewage sludge and biosolids can also be an important source by which pharmaceuticals and other emerging organic contaminants pass to the environment, when these products are landfilled or applied to land as an example of beneficial reuse (eg, as nutrient sources/fertilisers for agricultural or forestry applications) (van der Kroght 2018; Wang et al. 2018).

3.3.1 Biosolids

Analysis of aged biosolids from Kaikōura for a range of commonly-prescribed pharmaceuticals detected 27 of the 65 target compounds, including analgesics (naproxen, acetaminophen), lipid regulators and statins (fenofibrate), psychiatric drugs (carbamazepine), antibiotics (sulfamethoxazole, ciprofloxacin) and beta blockers (metoprolol, propranolol). The concentrations of pharmaceutical residues were determined to be lower than reported elsewhere for fresh biosolids, which was likely the result of continued degradation of compounds during extended storage and stabilisation (CIBR 2013).

Preliminary results from another New Zealand study measured a range of pharmaceuticals in biosolids, and found that some commonly-used drugs like acetaminophen, diclofenac and metoprolol were detected at “relatively high levels” (CIBR 2014).

Gielen (2007) analysed sewage solids from Rotorua WWTP at different stages of treatment, detecting ibuprofen, carbamazepine, and 17α-ethinyl estradiol across the various samples. Wang et al. (2018) also analysed biosolids from the Rotorua WWTP for the presence of erythromycin, fluoxetine, carbamazepine, naproxen, and gemfibrozil, and detected all of the target pharmaceuticals, with an average concentration in the tens of ng/g (dry weight). The antimicrobial triclosan was also detected.

3.3.2 Aquatic environments (water and sediments)

Stewart and colleagues (Stewart 2013; Stewart et al. 2014) analysed estuarine sediments from 13 sites around the Auckland region, and determined that of 46 pharmaceuticals tested, 21 were present at concentrations sufficient for quantification, with a further 11 detected at trace levels. The analgesics acetaminophen and naproxen were present at much higher concentrations than other compounds (mean 7.7 ng/g and 5.5 ng/g, respectively); metoprolol, diclofenac, clarithromycin, fenofibrate, roxithromycin and ranitidine were present at 1-2 ng/g, with cimetidine, sotalol, clenbuterol, carbamazepine, salbutamol, hydrochlorothiazide, trimethoprim and bezafibrate averaging <1 ng/g. Hydrochlorothiazide, ranitidine, cimetidine, clarithromycin, roxithromycin and trimethoprim were the most widely distributed, being quantified at more than half the sites. The authors noted some site-specific influences; for example, one site that was previously part of a waste stabilisation pond facility had a high number of different compounds detected, while sites that were downstream of a WWTP outfall or that were known to be impacted by sewage overflow events had the highest concentrations of pharmaceutical contaminants. However, they also noted that the frequency of detection or concentration of pharmaceuticals may not necessarily reflect inputs into the immediate environment, as many pharmaceuticals do not partition strongly to sediments and would instead be present predominantly in the dissolved phase, and thus sampling of both waters and sediments would provide a more comprehensive understanding of their environmental presence.

Bernot et al. (2019) analysed surface water and sediments from 4 sites in Dunedin prior to and following the arrival of university students for Orientation Week. Of 32 EOCs assessed (including 21 human and 4 veterinary pharmaceuticals), carbamazepine (9.7-26 ng/L) was the only pharmaceutical detected in the dissolved phase, with no pharmaceuticals detected in sediments.

Emnet et al. (2020) analysed seawater, marine sediment and shellfish alongside WWTP effluents from three communities in Whakaraupō/Lyttleton Harbour. Although the study focused on non-pharmaceutical EOCs, they did analyse samples for steroid hormones. Although they reported intermittent detection of natural hormones including estrone, the synthetic estrogen 17α-ethinyl estradiol was not detected in any seawater or shellfish sample.

3.3.3 Groundwater

ESR leads a four-yearly survey for the presence of pesticides and other emerging organic contaminants in groundwater. Close and Humphries (2019) reported that a number of pharmaceuticals, including acetaminophen, carbamazepine, diclofenac, ibuprofen, naproxen, mestranol and 17α-ethinyl estradiol, were detected during the 2018 survey. Groundwater samples were collected predominantly from rural areas, where the only plausible source of the pharmaceuticals was domestic wastewater from onsite wastewater management systems (OWMS) or small community WWTPs (B. Humphries, personal communication, July 2024). The findings of the 2022 survey are currently being finalised and are due for release towards the end of 2024, but preliminary results suggest pharmaceuticals, including antibiotics and analgesics, were again detected in shallow groundwater wells (B. Humphries, personal communication, July 2024).

Also in 2018, Moreau et al. (2019) undertook extensive analysis of EOCs in groundwater samples from across the Waikato region. Among the pharmaceutical contaminants detected were carbamazepine, celiprolol, diclofenac, atenolol, sotalol, sulfamethoxazole, tramadol and venlafaxine.

A small number of samples collected from shallow groundwater wells in proximity to an OWMS in Canterbury had detectable levels of acetaminophen and sulfamethoxazole (Humphries et al. 2024).

3.4 SUMMARY OF NEW ZEALAND DATA

Overall, the available data show that 57 different active pharmaceutical ingredients (including two API metabolites) have been detected in either untreated/influent municipal wastewater and/or treated municipal wastewater in Aotearoa New Zealand. Twenty-three of these APIs are amongst the 100 most commonly dispensed pharmaceuticals in New Zealand (based on the number of dispensings, as per Table 1). In addition, a further 32 compounds are strongly inferred as being present in wastewater by virtue of their presence in environmental samples, where the most plausible explanation for their presence is introduction via wastewater (ie, via discharge, overflows, leaks etc); five of these compounds were also among the most commonly dispensed pharmaceuticals in New Zealand.

The APIs most frequently detected in wastewaters were the analgesics and NSAIDs acetaminophen, diclofenac, ibuprofen and naproxen; the antibiotics sulfamethoxazole and trimethoprim; the anticonvulsant carbamazepine; beta blockers including atenolol and metoprolol; psychiatric medications including fluoxetine; the anti-hypertensive diltiazem; and steroids hormones estrone and 17α-ethinyl estradiol. These findings may, however, be somewhat biased by the small number of studies available and these APIs being amongst those most commonly targeted by analytical suites. Where quantifiable levels of pharmaceuticals were detected, concentrations ranged from several ng/L to tens of µg/L; in most cases, concentrations tended towards tens to hundreds of ng/L. However, concentrations varied widely both between compounds and for a compound across different studies; differences in the number of samples included in a given study, the way they were collected and analysed, and the way data was subsequently reported likely contributed to or exacerbated some of this variation. A number of studies include only single data points for each compound. It is therefore difficult to identify trends in prevalence or relative concentrations for different compounds.

Other than the analgesics and NSAIDs acetaminophen, diclofenac, naproxen and ibuprofen, and lidocaine (the first four also being highly prescribed medicines, and lidocaine also being used in surgical anaesthesia), none of the APIs listed in Table 2 as commonly being found in OTC therapies were reported as being detected in wastewater, almost certainly because no study to date has included them as target analytes.

3.5 PRESENCE OF PHARMACEUTICALS IN MUNICIPAL WASTEWATERS INTERNATIONALLY

In the absence of comprehensive information as to the presence of pharmaceuticals in wastewater in New Zealand, a summary of pharmaceuticals that are commonly detected in wastewaters in international studies has been compiled as a point of reference. Although several authors (Gaw et al. 2014; Tremblay and Northcott 2015; Stewart et al. 2016) have noted that the concentrations of representative EOC compounds (of which pharmaceuticals are a subset) in New Zealand wastewaters are similar to those reported internationally, there will also be differences that arise through factors such as unique regulatory or prescribing environments, population health and demographics, and general behaviours around medications that might influence usage patterns. Nonetheless, the data summarised in Table 5 provides some insights into what other pharmaceuticals might be expected in New Zealand wastewater, especially where compounds are widely used, as indicated by dispending data. For example, the following APIs are all identified as being highly dispensed in New Zealand (Table 1) and have been detected at various concentrations in international studies (Table 5), and therefore might reasonably be expected to be present in New Zealand wastewater: amoxicillin, chloramphenicol, amlodipine, atorvastatin, simvastatin, bendroflumethiazide, lorazepam, sertraline and pantoprazole. Several further APIs have been reported in high concentrations in wastewater overseas, including the antibiotics azithromycin, ciprofloxacin, erythromycin, oxytetracycline and vancomycin, anti-ulcer medications cimetidine and ranitidine, anti-hypertensives valsartan and lisinopril, the lipid regulator gemfibrozil and x-ray contrasts such as iohexol and iopromide, and might also be expected to be present in New Zealand wastewaters.

Table 5: Concentrations of pharmaceuticals detected in untreated influent and treated effluent wastewater, based on international literature.

Therapeutic group	Pharmaceutical compound	Concentration range (ng/L)		Concentration* mean (max) [%] (ng/L)	Reference
		Influent	Effluent	Effluent	
Analgesics/ NSAIDs	Acetaminophen	<MQL – 500,000	<MQL – 62,000		Tran et al. (2018)
		1,570 – 56,900	ND – 30		Luo et al. (2014)
				79 (1,500) [14]	Kositch et al. (2014)
		1,130 – 201,000	ND	ND [0]	Gracia-Lor et al. (2012)
		68,107– 482,687 108,383-246,641	1,826 – 24,525 <80 – 1,575	1,733 [100] 353 [86]	Kasprzyk-Hordern et al. (2009)
	Aspirin	485 – 2,042 1,321 – 5,448	<3 – 85 <3 – 65	27 [92] 20 [50]	Kasprzyk-Hordern et al. (2009)
	Codeine	<MQL – 32,295	<MQL – 15,593		Tran et al. (2018)
		1,732 – 32,295 2,496 – 12,599	2,940 – 15,593 1,457 – 4,178	5,271 [100] 2,716 [100]	Kasprzyk-Hordern et al. (2009)
	Diclofenac	<MQL – 4,869	<MQL – 5,164		Tran et al. (2018)
		<1 – 94,200	<1 - 690		Luo et al. (2014)
		260 – 1,490	60-740	33 (740) [100]	Gracia-Lor et al. (2012)
		26 – 257 57 – 1,161	33 – 142 6 – 496	98 [100] 179 [100]	Kasprzyk-Hordern et al. (2009)
	Fenoprofen	<MQL – 2,260	<MQL – 405		Tran et al. (2018)
	Ibuprofen	<MQL – 83,500	<MQL – 24,600		Tran et al. (2018)
		<4 – 603,000	ND – 55,000		Luo et al. (2014)
				260 (4,200) [46]	Kositch et al. (2014)
		2,280 – 39,800	<250	<250 [33]	Gracia-Lor et al. (2012)
		968 – 2,986 984 – 6,328	131 – 424 65 – 491	263 [100] 143 [100]	Kasprzyk-Hordern et al. (2009)
	Indomethacin	<MQL - 640	<MQL – 507		Tran et al. (2018)
	Ketoprofen	<MQL – 5,700	<MQL – 1,620		Tran et al. (2018)
		<4 – 8,560	<3 – 3,920		Luo et al. (2014)
		<70 – 1,170	150 – 620	300 (620) [100]	Gracia-Lor et al. (2012)
		<4 – 119 31 – 346	<3 – 33 7 – 37	16 [69] 18 [75]	Kasprzyk-Hordern et al. (2009)
	Mefenamic acid	<17 – 1,270	<5 – 390		Luo et al. (2014)
		<20 – 1,269 <17 – 32	<5 – 222 <5 – 103	61 [92] 39 [83]	Kasprzyk-Hordern et al. (2009)
	Naproxen	<MQL – 611,000	<MQL – 33,900		Tran et al. (2018)
		<2 – 52,900	<2 – 5, 090		Luo et al. (2014)
		270 – 3,580	<30 - 720	170 (720) [100]	Gracia-Lor et al. (2012)
		400 – 1,457 620 – 3,504	234 – 703 <2 – 269	370 [100] 170 [92]	Kasprzyk-Hordern et al. (2009)
	Salicylic acid	<MQL – 164,400	<MQL – 10,100		Tran et al. (2018)
		580 – 63,700	ND - 500		Luo et al. (2014)
		3,100 – 277,000	<430 – 236,000	<430 (236,000) [26]	Gracia-Lor et al. (2012)
		1,479 – 18,479 5,644 – 32,082	<1 – 497 <1 – 391	164 [92] 75 [83]	Kasprzyk-Hordern et al. (2009)
	Tramadol	8,505 – 89,026 23,037 – 85,843	24,132 – 97,616 12,779 – 56,810	43,813 [100] 28,147 [100]	Kasprzyk-Hordern et al. (2009)

Table 5 continued. Concentrations of pharmaceuticals detected in untreated influent and treated effluent wastewater, based on international literature.

Class	Pharmaceutical compound	Concentration range (ng/L)		Concentration mean (max) [%] (ng/L)	Reference
		Influent	Effluent	Effluent	
Antibiotics	Amoxicillin	<MQL – 6,516	<MQL – 16,70		Tran et al. (2018)
	Azithromycin	61 – 303,500	38 – 1,300		Tran et al. (2018)
	Ceftazidime	<MQL	<MQL		Tran et al. (2018)
	Chloramphenicol	<MQL – 2,430	<MQL – 1,050		Tran et al. (2018)
		<4 – 319 150 – 452	<6 <6 – 69	<6 [0] 21 50	Kasprzyk-Hordern et al. (2009)
	Chlortetracycline	<MQL – 15,911	<MQL – 1,986		Tran et al. (2018)
	Ciprofloxacin	<MQL – 246,100	<MQL – 5,692		Tran et al. (2018)
				67 (260) [61]	Kositch et al. (2014)
	Clarithromycin	<MQL – 8,000	48 – 7,000		Tran et al. (2018)
	Clindamycin	<MQL – 101	2.9 – 180		Tran et al. (2018)
	Enrofloxacin	<MQL – 250	<MQL – 636		Tran et al. (2018)
	Erythromycin	<MQL – 2,130	<MQL – 290		Tran et al. (2018)
		140 – 10,000	20 – 2,840		Luo et al. (2014)
		242 – 6,755 144 – 10,025	292 – 2,841 23 – 2,772	1,385 [100] 696 [100]	Kasprzyk-Hordern et al. (2009)
	Erythromycin-H_2O	<MQL – 20,600	<MQL – 14,400		Tran et al. (2018)
	Lincomycin	<MQL – 19,401	<MQL – 21,278		Tran et al. (2018)
				ND [0]	Kositch et al. (2014)
	Meropenem	265 – 433	27 – 68		Tran et al. (2018)
	Minocycline	<MQL – 3,808	<MQL		Tran et al. (2018)
	Ofloxacin	55 – 1,274	<MQL – 8,637		Tran et al. (2018)
				160 (660) [90]	Kositch et al. (2014)
	Oxytetracycline	<MQL – 47,000	<MQL – 4,200		Tran et al. (2018)
	Sulfadimethoxine			ND [0]	Kositch et al. (2014)
	Sulfamethazine	<MQL – 1,814	<MQL – 363		Tran et al. (2018)
				12 (87) [2]	Kositch et al. (2014)
	Sulfamethoxazole	<MQL – 11,555	<MQL – 1,800		Tran et al. (2018)
		<3 - 980	<3 – 1,150		Luo et al. (2014)
				910 (2,900) [80]	Kositch et al. (2014)
		<3 – 150 20 – 274	<3 – 23 4 – 44	10 [82] 19 [100]	Kasprzyk-Hordern et al. (2009)
	Tetracycline	<MQL – 48,000	<MQL – 3,600		Tran et al. (2018)
	Trimethoprim	<MQL – 6,796	<MQL – 37,000		Tran et al. (2018)
		60 – 6,800	<10 – 3,050		Luo et al. (2014)
				170 (370) [86]	Kositch et al. (2014)
		464 – 6,796 1,514 – 4,673	625 – 3,052 385 – 1,218	1,152 [100] 876 [100]	Kasprzyk-Hordern et al. (2009)
	Tylosin	<MQL – 1,500	<MQL – 720		Tran et al. (2018)
	Vancomycin	962 – 43,740	<MQL – 8,514		Tran et al. (2018)
Anti-asthmatic	Salbutamol			14 (35) [54]	Kositch et al. (2014)
		<2 – 321 50 – 150	<1 – 234 <1 – 22	63 [88] 10 [86]	Kasprzyk-Hordern et al. (2009)
	Theophylline			<RL [8]	Kositch et al. (2014)

Table 5 continued. Concentrations of pharmaceuticals detected in untreated influent and treated effluent wastewater, based on international literature.

Class	Pharmaceutical compound	Concentration range (ng/L)		Concentration mean (max) [%] (ng/L)	Reference
		Influent	Effluent	Effluent	
Anti-convulsants	Carbamazepine	<MQL – 18,500	<MQL – 4,596		Tran et al. (2018)
		<40 – 3,780	<5 – 4,600		Luo et al. (2014)
				97 (240) [96]	Kositch et al. (2014)
		709 – 2,930 104 – 3,110	644 – 4,596 152 – 2,324	2,499 [100] 826 [100]	Kasprzyk-Hordern et al. (2009)
	Gabapentin	4,825 – 25,079	213 – 56,810		Tran et al. (2018)
		2,059 – 37,426 10,674 – 25,079	3,001 – 42,611 1,786 – 3,514	15,747 [100] 2,529 [100]	Kasprzyk-Hordern et al. (2009)
Antihistamines	Cimetidine	733 – 130,57 680 – 6,509	828 – 9,395 253 – 781	2,605 [100] 462 [100]	Kasprzyk-Hordern et al. (2009)
	Promethazine			ND [0]	Kositch et al. (2014)
	Ranitidine			120 (1,400) [38]	Kositch et al. (2014)
		<10 – 11,664 2,005 – 11,153	<9 – 455 15 – 783	224 [75] 425 [100]	Kasprzyk-Hordern et al. (2009)
Anti-hypertensive	Amlodipine			6.9 (18) [22]	Kositch et al. (2014)
	Clonidine			ND [0]	Kositch et al. (2014)
	Diltiazem			85 (340) [82]	Kositch et al. (2014)
		228 – 3,207 405 – 5,258	95 – 642 108 – 1,156	267 [100] 357 [100]	Kasprzyk-Hordern et al. (2009)
	Enalapril			13 (32) [27]	Kositch et al. (2014)
		20-290	ND	ND [0]	Gracia-Lor et al. (2012)
	Enalaprilat			14 (150) [10]	Kositch et al. (2014)
	Lisinopril			814 (3,300) [47]	Kositch et al. (2014)
	Norverapamil[a]			5.8 (20) [52]	Kositch et al. (2014)
	Valsartan			1,600 (5,300) [98]	Kositch et al. (2014)
		132 – 1,660 354 – 5,388	<5 – 71 6 – 711	192 [92] 275 [100]	Kasprzyk-Hordern et al. (2009)
	Verapamil			26 (97) [80]	Kositch et al. (2014)
Anti-thrombotic	Warfarin			ND [0]	Kositch et al. (2014)
β blockers	Atenolol	<MQL – 294,000	<MQL – 14,200		Tran et al. (2018)
		100 – 33,100	130 – 7,600		Luo et al. (2014)
				940 (3,000) [96]	Kositch et al. (2014)
		3,090 – 33,106 8,102 – 25,146	1,260 – 7,602 1,292 – 3,168	2,870 [100] 2,123 [100]	Kasprzyk-Hordern et al. (2009)
	Metoprolol	<MQL – 79,500	<MQL – 5,762		Tran et al. (2018)
		2 – 1,520	3 - 250		Luo et al. (2014)
				410 (66) [98]	Kositch et al. (2014)
		39-117 56 – 146	35 – 130 34 – 57	69 [100] 41 [100]	Kasprzyk-Hordern et al. (2009)
	Propranolol	<MQL – 1,962	<MQL – 615		Tran et al. (2018)
				33 (260) [88]	Kositch et al. (2014)
		125 – 1,962 110 – 1,946	121 – 405 130 – 523	265 [100] 264 [100]	Kasprzyk-Hordern et al. (2009)

Table 5 continued. Concentrations of pharmaceuticals detected in untreated influent and treated effluent wastewater, based on international literature.

Class	Pharmaceutical compound	Concentration range (ng/L)		Concentration mean (max) [%] (ng/L)	Reference
		Influent	Effluent	Effluent	
Blood lipid-regulators and statins	Atorvastatin			<RL [8]	Kositch et al. (2014)
		<7 - 450	10 - 160	20 (160) [76]	Gracia-Lor et al. (2012)
	Bezafibrate	17 – 7,600	<MQL – 4,800		Tran et al. (2018)
		50 – 1,390	30 – 670		Luo et al. (2014)
		209 – 1,391 135 – 1,285	<85 - 667 <94 – 393	231 [92] 177 [92]	Kasprzyk-Hordern et al. (2009)
		20 - 460	20 - 390	70 (390) [100]	Gracia-Lor et al. (2012)
	Clofibric acid	<MQL - 266	<MQL – 91		Tran et al. (2018)
		0 – 740	ND – 330		Luo et al. (2014)
		<1 – 57 <1 – 12	<1 – 75 <1 – 48	15 [62] 6 [25]	Kasprzyk-Hordern et al. (2009)
	Gemfibrozil	<MQL – 36,530	<MQL – 5,233		Tran et al. (2018)
		100 – 17,00	<2.5-5,240		Luo et al. (2014)
				120 (2,300) [76]	Kositch et al. (2014)
		160 – 2,120	150 – 1,240	540 (1,240) [100]	Gracia-Lor et al. (2012)
	Pravastatin	140 - 240	70 – 170	100 (170) [30]	Gracia-Lor et al. (2012)
		<60 <60	<60 <60	<60 [0] <60 [0]	Kasprzyk-Hordern et al. (2009)
	Simvastatin			<RL [24]	Kositch et al. (2014)
		<7 – 798 <7	<3 – 20 <3	5 [38] <3 [0]	Kasprzyk-Hordern et al. (2009)
Corticosteroid	Hydrocortisone			ND [0]	Kositch et al. (2014)
	Fluocinonide			ND [0]	Kositch et al. (2014)
	Fluticasone			ND [0]	Kositch et al. (2014)
	Methylprednisolone			ND [0]	Kositch et al. (2014)
	Prednisolone			ND [0]	Kositch et al. (2014)
	Prednisone			ND [0]	Kositch et al. (2014)
Diuretic	Bendroflumethiazide	<8 – 66 <8 - 101	<8 – 58 <8	11 [38] <8 [0]	Kasprzyk-Hordern et al. (2009)
	Furosemide			280 (810) [90]	Kositch et al. (2014)
		836 – 5,111 1,580 – 6,022	583 – 1,956 <43 – 1,823	1,161 [100] 629 [92]	Kasprzyk-Hordern et al. (2009)
	Hydrochlorothiazide			1,100 (2,800) [100]	Kositch et al. (2014)
	Triamterene			37 (170 [70]	Kositch et al. (2014)
Opioids and illicit substances	Hydrocodone			22 (92) [44]	Kositch et al. (2014)
	Oxycodone			53 (310) [60]	Kositch et al. (2014)
	Propoxyphene			17 (34) [25]	Kositch et al. (2014)
Psychiatric drugs	Amitriptyline			11 [(10) [40]	Kositch et al. (2014)
		341 – 5,143 504 – 6,711	53 – 357 <2 – 335	197 [100] 85 [71]	Kasprzyk-Hordern et al. (2009)
	Alprazolam			10 (31) [30]	Kositch et al. (2014)
		ND	<10	<10 [38]	Gracia-Lor et al. (2012)
	Desmethylsertraline[b]			9.9 (24) [18]	Kositch et al. (2014)

Table 5 continued. Concentrations of pharmaceuticals detected in untreated influent and treated effluent wastewater, based on international literature.

Class	Pharmaceutical compound	Concentration range (ng/L)		Concentration mean (max) [%] (ng/L)	Reference
		Influent	Effluent	Effluent	
Psychiatric drugs	Fluoxetine			8.7 (31) [38]	Kositch et al. (2014)
	Lorazepam	ND	30 - 60	40 (30) [55]	Gracia-Lor et al. (2012)
	Norfluoxetine[c]			7.7 (15) [17]	Kositch et al. (2014)
	Olanzapine	ND	ND	ND[0]	Gracia-Lor et al. (2012)
	Paroxetine			ND [0]	Kositch et al. (2014)
		ND	ND	ND [0]	Gracia-Lor et al. (2012)
	Risperidone	ND	ND	ND[0]	Gracia-Lor et al. (2012)
	Sertraline			21 (71) [64]	Kositch et al. (2014)
	Sulpiride	65 – 15,359	33 – 322		Tran et al. (2018)
	Venlafaxine	40 - 520	60 - 300	140 (300) [100]	Gracia-Lor et al. (2012)
Steroid hormones	Estrone	<MQL - 670	<MQL – 95		Tran et al. (2018)
		10 - 170	<1 – 80		Luo et al. (2014)
	Estriol	<MQL - 802	<MQL – 275		Tran et al. (2018)
		125 - 800	ND		Luo et al. (2014)
	Estradiol	2 - 50	<1 - 7		Luo et al. (2014)
	17a-ethinylestradiol	<MQL - 242	<MQL – 106		Tran et al. (2018)
	Progesterone			<RL [2]	Kositch et al. (2014)
	Testosterone			ND [0]	Kositch et al. (2014)
X-ray contrasts	Iohexol	64 – 124,966	1200 – 9,237		Tran et al. (2018)
	Iopromide	<MQL – 12,200	<MQL – 9,300		Tran et al. (2018)
	Iopamidol	83 – 45,611	<MQL – 6,520		Tran et al. (2018)
Other	Amphetamine			3.5 (40) [10]	Kositch et al. (2014)
	Benztropine			ND [0]	Kositch et al. (2014)
	Digoxin	<538 <538	<268 <268	[0] [0]	Kasprzyk-Hordern et al. (2009)
	Mesalamine	841 – 2,828 3,160 – 27,490	1,417 – 3,072 <172 – 1218	2,111 [100] 630 [86]	Kasprzyk-Hordern et al. (2009)
	Metronidazole	158 – 1,583 347 – 962	60 – 421 129 – 561	265 [100] 353 100	Kasprzyk-Hordern et al. (2009)
	Omeprazole	ND	ND	ND[0]	Gracia-Lor et al. (2012)
	Pantoprazole	ND	50 - 180	130 (180) [65]	Gracia-Lor et al. (2012)
	Sulfasalazine	<80 – 447 0.05 – 0.4	100 – 2,185 0.5 – 1.5	484 [100] 0.3 [100]	Kasprzyk-Hordern et al. (2009)
	Sulfapyridine	26 – 5,763 2,164 – 12,397	127 – 378 94 – 1,112	277 [100] 455 [100]	Kasprzyk-Hordern et al. (2009)

MQL – minimum quantification limit; ND – not detected;

[a] Active metabolite of verapamil.

[b] Active metabolite of sertraline.

[c] Active metabolite of fluoxetine,

NOTE: Data from are presented in the literature differently, some authors reporting the range of concentrations reported (ie minimum and maximum values), some reporting mean values, and some providing information on the percentage of samples analysed that are positive for the target pharmaceutical compounds or analyte. These data have been summarised here as best as possible, with the use of parentheses and square brackets used to differentiate mean values and detection rates (ie as % positive samples) where this data was provided.

4. REMOVAL OF PHARMACEUTICALS FROM MUNICIPAL WASTEWATER IN NEW ZEALAND

Wastewater treatment aims to remove contaminants from influent wastewater, to produce an effluent that can be discharged to the environment without causing adverse impacts on ecological or human health, or in some situations, is appropriate for certain re-use applications. Wastewater treatment usually features a mixture of physical, biological and/or chemical treatment techniques, that can be incorporated into four key stages: preliminary treatment, primary treatment, secondary treatment and tertiary treatment (von Sperling 2007; Peake et al. 2016; Beca et al. 2020). The level of treatment (ie, primary, secondary, tertiary) and specific processes installed at a WWTP will depend on the size and nature of the community/catchment served (eg, residential, industrial and/or agricultural contributions), the volume and characteristics of the wastewater to be treated, and other considerations of the local context such as climate, geography, receiving environment and/or cultural considerations. As different treatment technologies vary in their ability to remove different contaminant groups from the wastewater stream, the presence of certain contaminants (including pharmaceuticals) in wastewater effluents will be influenced by the treatment processes and operational parameters in place.

Preliminary treatment involves the removal of course solids, debris and grit to protect downstream processes and equipment.

Primary treatment removes a large proportion of suspended solids and organic matter (measured as biochemical oxygen demand, BOD), largely through sedimentation. Primary treated effluents usually undergo further treatment within the WWTP, while the sludge produced by settled materials may be landfilled, incinerated, or further treated.

Secondary treatment involves the further removal of remaining suspended solids and biodegradable organic matter (dissolved and colloidal) through biological processes. Microorganisms (eg, bacteria and protozoa) present in secondary treatments consume organic matter present in the wastewater and convert it to biomass as they grow and reproduce.

Tertiary treatment, sometimes also called advanced treatment or effluent polishing, is designed to further stabilise and improve effluent quality before discharge to the environment. More than one tertiary treatment process may be used in order to target removal of specific contaminant(s) (eg nutrients, toxic metals) that are not well-removed by previous treatment stages.

In addition, ‘quaternary treatments’ are being developed as highly advanced treatment options intended to remove the large array of emerging contaminants and micropollutants that are increasingly recognised as present at trace levels in urban wastewater, but which are not removed by conventional secondary or tertiary treatment processes. The uptake of

these processes beyond certain jurisdiction (eg, some parts of the European Union[13,14]) or niche applications is limited due to the high costs associated with their construction and operation – constraints that also limit the implementation of tertiary-level treatment (Gracia-Lor et al. 2012; Luo et al. 2014). Further information on some of these treatment processes is provided in Appendix C.

4.1 MUNICIPAL WASTEWATER TREATMENT PROCESSES AND TECHNOLOGIES USED IN AOTEAROA NEW ZEALAND

As a part of the recent Wastewater Sector Review, a stocktake of municipal wastewater treatment plants determined that there were 318 municipal WWTPs currently in use in New Zealand (Becca et al. 2020). The majority of these WWTPs service small populations (ie, fewer than 5,000 people), such that 78% of WWTPs service just 6% of the serviced population[15], with the majority of the serviced population is connected to a so-called large or major plant (Table 6). The estimated total wastewater flow for all of New Zealand's WWTPs is approximately 1.5 million m^3 (1.5 billion litres) per day, of which an estimated 29% comes from the Auckland region, followed by Canterbury (16%) and Wellington (13%).

Table 6: Number of wastewater treatment plants in New Zealand, based on the size of the serviced population.

WWTP class size	No. of plants	% population serviced
<1,000	248	1
1,001 – 5,000		5
5,001 – 10,000	26	4
10,001 – 100,000	44	34
>100,000		54

Reproduced from Beca et al. (2020).

[13] https://www.europarl.europa.eu/news/en/press-room/20240408IPR20307/new-eu-rules-to-improve-urban-wastewater-treatment-and-reuse
[14] https://www.europarl.europa.eu/doceo/document/TA-9-2024-0222_EN.html#title1
[15] 'Serviced population' describes the New Zealand population that is connected to a reticulated wastewater network and treatment system.

For those WWTPs where data is available on the receiving environment to which treated wastewater effluents are discharged, 143 WWTPs discharge effluents to a river, 109 discharge to land, and 64 discharge to sea (Figure 1). When the distribution across receiving environments is considered on a population basis, 74% of the serviced population are connected to a wastewater network that discharges to the sea, reflecting the coastal locations of New Zealand's main centres. A further 16% of the serviced population are connected to a network that discharges to a river, and 8% to a network that discharges to land (Beca et al. 2020). An estimated 21% of the New Zealand population is not connected to a reticulated wastewater network, but is instead connected to an OWMS, such as a septic tank that discharges to a localised drainage field (Beca et al. 2020).

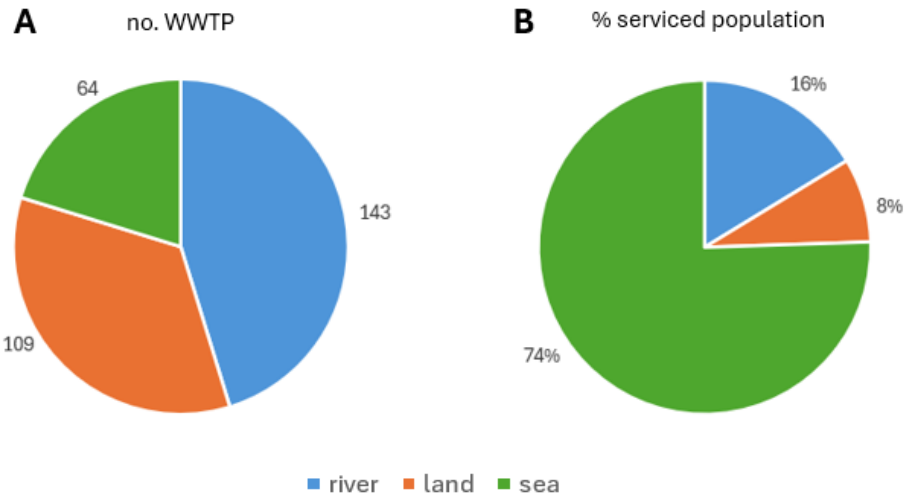


Figure 1: Receiving environment (river, land, sea) to which WWTPs in New Zealand discharge treated effluents. Shown as a) the number of total treatment plants discharging to each environment, and b) the proportion of serviced population connected to a plant that discharges to each environment.

A variety of wastewater treatment technologies are used in New Zealand, including activated sludge (AS) processes, tricking filters, aerated lagoons, facultative waste stabilisation ponds and recirculating filters (Table 7). The majority of WWTPs in New Zealand are waste stabilisation ponds; their simple construction and operation meant they were the common form of wastewater treatment system constructed between the 1960s and 1980s (Peake et al. 2016; Water NZ 2017; Beca et al. 2020). These systems are more commonly associated with smaller centres, so despite accounting for 64% of systems, they serve approximately 17% of the serviced population (Beca et al. 2020). Activated sludge and biofilm processes, which are able to provide a greater level of treatment than stabilisation ponds, wetlands or lagoons, are the main type of secondary treatment used in newly constructed WWTPs and those in larger population centres; approximately 74% of the serviced population is connected to a system that utilises activated sludge (Beca et al. 2020). Although pond-based

systems provide secondary treatment and can be efficient in removing BOD, many are being retrofitted with upgrades to improve their ability to remove other wastewater constituents (especially nutrients) and thus improve the quality of their discharge, such as including additional or improved aeration, addition of in-pond media to support biofilm growth, membrane filtration, or conversion to AS processes by converting an existing pond to an AS reactor or construction of a compact reactor adjacent to existing ponds (Beca et al. 2020).

There is continuing research and development of new and emerging wastewater treatment processes. Key drivers of this work include growing awareness of the presence of emerging contaminants in wastewaters effluents and their potential risk to aquatic environments, as well as a shift towards ‘circular economy thinking’ with a focus on resource recovery (eg, biowastes, gaseous byproducts, final wastewater) and reduced footprint (eg, energy consumption, land requirement, carbon footprint) (Beca et al. 2020).

Table 7: Overview of the different types of technologies used in New Zealand wastewater treatment plants.

Treatment	WSAA Group*	Classification	Examples	No. of facilities	% of facilities	% serviced population
Activated sludge	Type 1	AS processes with primary treatment, digesters and on-site cogeneration	Mangere, Chapel Street (Tauranga)	5	2	48.7
	Type 2	AS processes with primary treatment, digesters and no onsite cogeneration	Westport	1	<1	0.1
	Type 3	AS processes with no primary treatment nor anaerobic digesters	Moa Point (Wellington), Shotover (Queenstown)	51	16	25.1
Trickling filters	Type 4.1	Tricking filters	Taupo	22	7	7.9
	Type 4.2	Tricking filters combined with AS process	Tokoroa	4	1	2.4
Waste stabilisation ponds and lagoons	Type 5.1	Aerated lagoons and oxidation ponds with high intensity aeration	Blenheim	37	11	6.2
	Type 5.2	Facultative ponds and wetlands	Huntly	168	53	9.3
Others	Type 6	Recirculating filters	Whakamaru	17	5	0.1
	Others	Septic tanks, Imhoff tanks, worm farms	Oamaru Bay	16	5	0.2

AS – activated sludge. * Water Services Association of Australia (WSAA) technology groupings are used to benchmark energy efficiency for similar process configurations.

Reproduced from Beca et al. (2020).

4.2 REMOVAL OF PHARMACEUTICALS FROM NEW ZEALAND WASTEWATER

Of the few studies that have assessed the presence of pharmaceuticals in wastewater in Aotearoa New Zealand, only two appear to have assessed the removal of these compounds by the respective wastewater treatment plant. In the context of the following discussion on removal of pharmaceuticals, removal generally refers to the loss of a parent compound from the aqueous phase as it moves through the treatment plant (ie, the difference between concentrations in influent and effluent wastewaters due to sorption to solids with subsequent sedimentation, biodegradation/biotransformation, sorption to biomass/floc and sedimentation to secondary sludge, etc) (Jelic et al., 2011; Verlicchi et al. 2012). However, this does not imply that pharmaceuticals accumulating in sludge will be subsequently degraded, and appropriate management of sludges and biowastes is required to prevent API release to the environment (Gracia Lor et al. 2012).

Gielen (2007) estimated the removal of several pharmaceuticals from wastewater at the Rotorua WWTP that used preliminary screening and grit settling, primary clarifiers and a five-stage activated sludge process that was optimised for nutrient removal, especially phosphorous (Gielen et al. 2009). They observed removal rates for the combined primary and AS processes ranging from 95% for salicylic acid and 85% for ibuprofen, to no removal of carbamazepine (Table 8). Carbamazepine concentrations appeared to increase during the treatment process, as has been observed in other studies (Castiglioni et al. 2006), likely due to the conversion of carbamazepine conjugates back to parent carbamazepine. The higher removal rates observed for other compounds together with generally low concentrations in solids suggest that microbial degradation played a major role in the removal of these compounds, although a small proportion of ibuprofen was partitioned to solids.

Kumar et al. (2019) assessed the removal of pharmaceuticals from a WWTP utilising primary treatment followed by parallel secondary treatment trains of five-stage Bardenpho and a membrane bioreactor (MBR). The Bardenpho process consisted of anaerobic, anoxic, aerobic, anoxic and aerobic zones for enhanced nutrient removal, with the MBR being a combination of membrane filtration and biological treatment. Overall, removal efficiency was very high for acetaminophen, ibuprofen (both >99%), clarithromycin, roxithromycin and naproxen (>90%). Average removal efficiencies for sulfamethoxazole, atenolol, fluoxetine, were in the range of 50-70%, and less than 50% for trimethoprim and metoprolol. There was very poor removal of diclofenac, and negative removal of carbamazepine, as reported elsewhere, likely due to enzymatic deconjugation of metabolites to release the parent compound. Removal rates for pharmaceuticals during each of the three separate treatment processes (ie, primary, Bardenpho and MBR) are shown in Table 9. Overall, primary treatment was not very efficient in removing pharmaceuticals, with removal rates ranging from <1% for trimethoprim to 37% for clarithromycin. Bardenpho and MBR processes appeared similarly effective in removing the total PPCP load: similar removal efficiencies were observed for acetaminophen and ibuprofen (both >99%), with lower but similar efficiencies between the two treatments for the removal of trimethoprim, clarithromycin, sulfamethoxazole, roxithromycin and fluoxetine. Bardenpho was more effective in the removal of metoprolol, atenolol and naproxen.

Table 8: Estimated removal rates for several pharmaceuticals from wastewater treated using primary clarification and secondary activated sludge processes.

Class	Pharmaceutical compound	Estimated removal %
Analgesic and NSAIDs	Ibuprofen	85
	Naproxen	76
	Salicylic acid	95
Anti-convulsant	Carbamazepine	0
Anti-hypertensive	Diltiazem	67
Steroid hormone	Ethinylestradiol	83

Data from Gielen (2007)

Table 9: Estimated removal rates for pharmaceuticals from an undisclosed WWTP utilising primary treatment with parallel 5-stage Bardenpho and MBR secondary treatments.

Class	Pharmaceutical compound	Estimated removal %	Treatment stage
Analgesic and NSAIDs	Acetaminophen	3 100 100	Primary treatment MBR 5-stage Bardenpho
	Diclofenac	28 14 <1	Primary treatment MBR 5-stage Bardenpho
	Ibuprofen	13 100 100	Primary treatment MBR 5-stage Bardenpho
	Naproxen	18 78 100	Primary treatment MBR 5-stage Bardenpho
Antibiotics	Clarithromycin	37 89 90	Primary treatment MBR 5-stage Bardenpho
	Roxithromycin	31 85 94	Primary treatment MBR 5-stage Bardenpho
	Sulfamethoxazole	3 58 62	Primary treatment MBR 5-stage Bardenpho
	Trimethoprim	<1 36 35	Primary treatment MBR 5-stage Bardenpho
Anti-convulsant	Carbamazepine	13 <1 <1	Primary treatment MBR 5-stage Bardenpho
Beta blockers	Atenolol	15 59 73	Primary treatment MBR 5-stage Bardenpho
	Metoprolol	36 23 38	Primary treatment MBR 5-stage Bardenpho
Psychiatric drug	Fluoxetine	14 56 48	Primary treatment MBR 5-stage Bardenpho

Data from Kumar et al. (2019)

4.3 REMOVAL OF PHARMACEUTICALS FROM WASTEWATER

Considering the limited data available on the removal of pharmaceuticals from wastewater in Aotearoa New Zealand, an overview of the main mechanisms by which pharmaceuticals tend to be removed, and a summary of removal rates as reported in the international literature has been included, which could support inferences as to which pharmaceuticals are or are not removed during wastewater treatment in New Zealand. The following discussion largely relates to conventional wastewater treatment processes such as conventional activated sludge (CAS) or waste stabilisation ponds and wetlands, since these are key treatment processes used in New Zealand (by population and number of individual WWTPs, respectively).

The fate of different pharmaceuticals through a WWTP is highly dependent on the physicochemical characteristics of the compound (eg, hydrophobicity, sorption affinity, biodegradability, volatility) and the type of treatment process and operational parameters (eg, specific types and configurations of secondary or tertiary treatment, specific microorganisms present in biological treatment, hydraulic and sludge retention times) (Verlicchi et al. 2012; Luo et al. 2014; Margot et al. 2015; Vinayagam et al. 2022). Some pharmaceuticals tend to be well removed during wastewater treatment, while others are only partially removed or not removed at all; observed removal efficiencies can vary across a wide range for different compounds (literally from 0 to 100%), as well as for the same compounds by different treatment methods. Further, removal efficiencies can differ between WWTPs using similar technologies but different operational conditions (eg, temperature, redox conditions, hydraulic and solids retention times) or within a plant over time (eg, due to seasonal variation) (Castiglioni et al. 2006; Verlicchi et al. 2012). Margot et al. (2015) estimated that on average, the majority of pharmaceuticals studied to date are removed by conventional treatment systems by less than 50%.

4.3.1 Mechanisms of removal

The main mechanisms for the removal of organic micropollutants during conventional wastewater treatment are i) sorption to particulate matter (ie, sludge), ii) biological transformation, iii) volatilisation, and iv) abiotic degradation. For pharmaceuticals, sorption and biological treatment are the two main mechanisms of removal, although the relative importance of each is highly variable between APIs (Verlicchi et al. 2012; Margot et al. 2015).

Sorption

Absorption to sludge or particulate matter can be an important removal mechanism for lipophilic, hydrophobic or positively charged micropollutants in wastewater, especially if they are poorly biodegradable (Margot et al. 2015). Pharmaceuticals with high partition coefficients between their dissolved and solid phases and that therefore have a greater tendency to sorb to sludge are often more readily removed by primary treatment (ie, through primary sedimentation) or possibly secondary treatment (ie, through sorption to and settling of floc) (Radjenovic et al. 2009). Conversely, some compounds may also sorb to colloidal particles (1 nm to 1 µm), which are considered part of the dissolved phase, effectively increasing the solubility of hydrophobic substances and limiting their removal by adsorption onto sludge (Margot et al. 2015). Although relatively high rates of removal by sorption (>60%) are observed for compounds including glenclibamide, fenofibrate, hydrochlorothiazide and quinolone antibiotics (eg, ciprofloxacin, norfloxacin, enrofloxacin),

most pharmaceuticals have high solubility, low hydrophobicity and often are negatively charged at neutral pH, conferring a low sorption affinity and meaning removal by sorption is often negligible (<5%) (Jelic et al. 2011; Verlicchi et al. 2012; Margot et al. 2015).

Biotransformation

The majority of pharmaceuticals have a high solubility and are therefore largely present in the dissolved phase; for these compounds, biological transformation or degradation is the main removal mechanism during conventional wastewater treatment. They may be completely degraded to carbon dioxide and water (known as mineralisation), or partially degraded to a range of metabolites/byproducts (Luo et al. 2014; Margot et al. 2015). The fraction of the pharmaceutical removed by biodegradation (either by direct metabolism and/or co-metabolism) during secondary treatment depends on the amount and types of microorganisms present (especially for activated sludge processes, where the use of specific microorganisms can be used to promote the degradation of certain types of contaminants), the biodegradability of the individual compound, and hydraulic retention times, as well as being influenced by temperature (warmer temperatures increase bacterial metabolic activity), pH, redox conditions and availability of co-substrates (Margot et al. 2015). Pharmaceuticals within the same therapeutic group can show significant variability in biodegradability. For example, amongst NSAIDs, diclofenac typically shows low biodegradation (<35%), where ibuprofen and ketoprofen tend to be degraded to a much higher extent (often >75%) (Salgrado et al. 2012; Luo et al. 2014). Many antibiotics exhibit low rates of biodegradation due to their inherent antimicrobial properties (Loos et al. 2013), while highly halogenated compounds such as fluoxetine are also resistant to biological treatment (Loos et al. 2013).

Some pharmaceuticals may show ‘negative removal’ during biological processes (ie effluent concentrations that are higher than influent concentrations). For example, the increase in diclofenac that is commonly observed is likely due to enzymatic deconjugation of glucuronidated or sulphated diclofenac (Verlicchi et al. 2012). Similarly, several studies have reported the apparent negative removal of estrone, likely due to the oxidation of estradiol to yield estrone, together with the deconjugation of other estrogens present in wastewater (D’Ascenzo et al. 2003; Verlicchi et al. 2012). Negative removal may also result where pharmaceuticals excreted primarily in faeces (eg macrolide antibiotics) are released from particulate matter during biological treatment processes, resulting in an apparent increase in load (Lindberg et al. 2005; Verlicchi et al. 2012). However, some cases of apparent negative removal may be due to the inherent variability between wastewater samples, instrumental error associated with trace-level concentrations, or sampling variation where the time between influent and effluent samples being collected does not reflect residence times within the plant (Clara et al. 2005; Verlicchi et al. 2012; MacDonald 2018).

Volatilisation

Volatilisation of wastewater contaminants can occur as surface volatilisation or stripping during aeration, and depends on the volatility of the compound (ie, Henry’s law constant, K_H) and operational parameters such as aeration, agitation and temperature (Margot et al. 2015). As pharmaceuticals have a low volatility, their removal by volatilisation is expected to be negligible (Luo et al. 2014; Margot et al. 2015).

Abiotic degradation

Some organic micropollutants are degraded during wastewater treatment by abiotic reactions such as photolysis or hydrolysis (Luo et al. 2014; Margot et al. 2015). However, photolytic degradation is typically low in conventional WWTPs, as low surface-to-volume ratio and high turbidity limits UV/light penetration. Hydrolysis is generally considered a negligible removal mechanism for most pharmaceuticals, apart from some β-lactam, macrolide and tetracycline antibiotics (Margot et al. 2015).

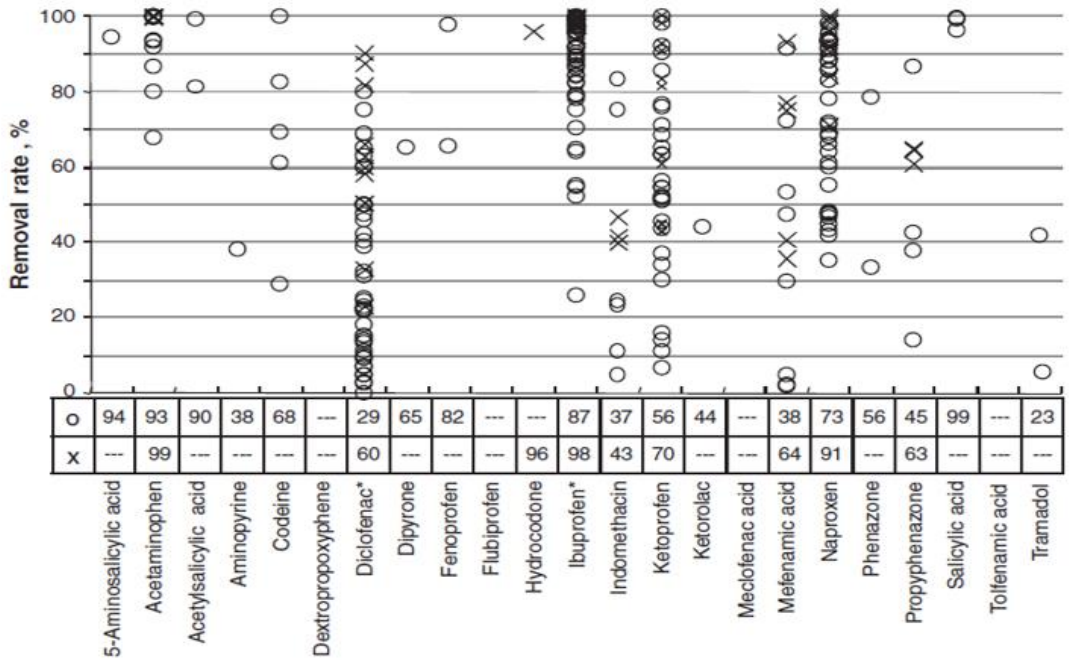
4.3.2 General trends in removal of pharmaceuticals

Verlicchi et al. (2012) reviewed data from 264 WWTPs across the world (mostly in Europe or North America) using conventional activated sludge treatment (CAS) and 20 WWTPs using membrane bioreactors (MBRs) for comparison, for the presence and removal of some 118 pharmaceutical compounds. Graphical summaries of the reported removal rates for various compounds are reproduced in Figures 2 to 4. These figures highlight that that while some compounds tend consistently towards being well-removed (eg, acetaminophen, ibuprofen) and others towards being poorly removed (eg, carbamazepine, clofibric acid), most exhibit a very wide spread in removal between different plants. Removal rates for an array of pharmaceuticals have also been collated from several further reviews, and are tabulated in Appendix D; these further demonstrate the wide range of removal rates observed for individual compounds across studies. Peake et al. (2016) also discuss the various processes contributing to the removal of several common pharmaceuticals during wastewater treatment.

In comparing the mean removal rates for compounds across wastewater treatment systems, Verlicchi et al. (2012) concluded that MBRs were capable of higher removal efficiencies than CAS systems, producing a higher quality effluent with respect to the presence of APIs. Similarly, Radjenovic et al. (2009) reported that pilot-scale MBRs enhanced the removal of multiple pharmaceutical residues that were poorly or moderately removed by a full-scale WWTP, including mefenamic acid, indomethacin, diclofenac, propyphenazone, pravastatin and gemfibrozil; however, other compounds showed similar removal between CAS and MBR (eg erythromycin, trimethoprim), while carbamazepine and hydrochlorothiazide were not removed by any treatment system. Other studies have shown that factors such as longer sludge retention times may have a significant impact on the removal of some pharmaceuticals, by allowing the growth of slower-growing microorganisms that are better able to degrade more complex molecules, but that the removal of other compounds may be reduced under such conditions (Radjenovic et al. 2009).

Tertiary treatments such as membrane filtration, activated carbon adsorption or advanced oxidative processes such as ozonation appear capable of removing a greater proportion of pharmaceuticals and producing a higher quality effluent compared with conventional treatments (Castiglioni et al. 2006; Gracia Lor et al. 2012; Luo et al. 2014; Oluwole et al. 2020; Vinayagam et al. 2022). However, many of these processes are not routinely used unless expressly required (eg, for certain reuse applications or protection of sensitive receiving environments) due to the high costs associated with their construction and operation (Luo et al. 2014; Vinayagam et al. 2022).

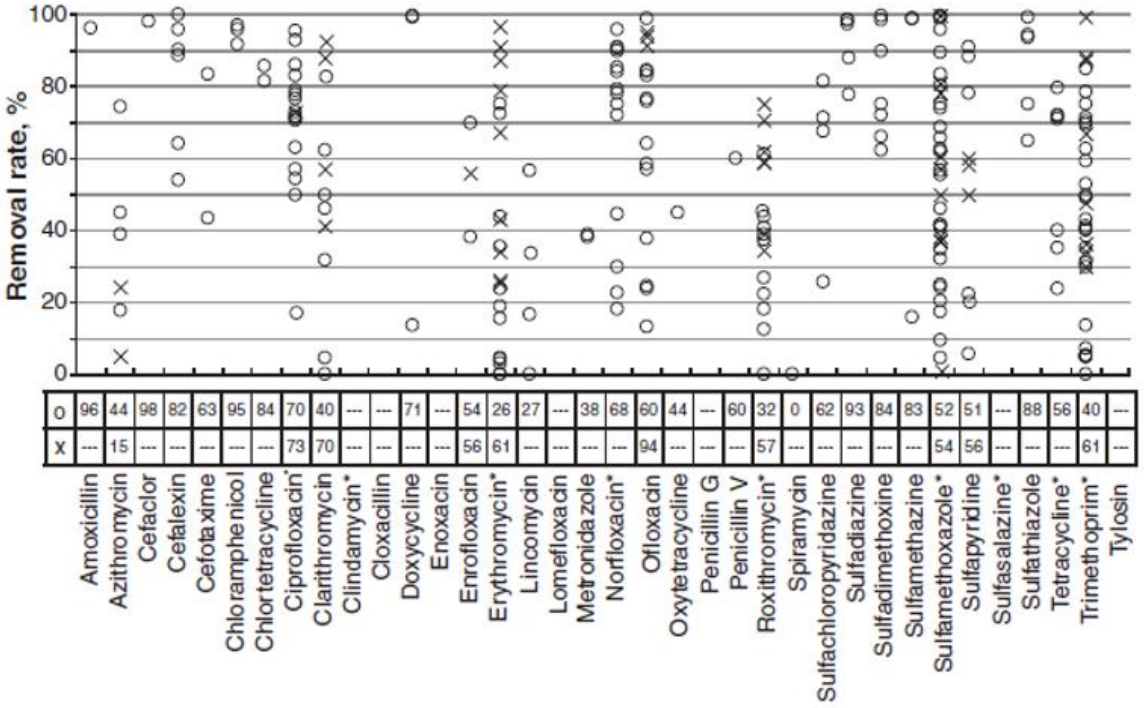
A



*Observed negative percentage removal efficiencies

Diclofenac: in CAS: -12, -11, -111; in MBR: -8, -7. Ibuprofen: in CAS: -4.4, -4.3, -13

B



*Observed negative removal efficiencies

Ciprofloxacin: in CAS: -44; Clindamycin: in CAS: -150; Erythromycin: in CAS: -84, -14, -11; Norfloxacin: in CAS: -6, Roxithromycin: in CAS: -4, -80, -32; Sulfamethoxazole: in CAS: -24; -20; Sulfasalazine: in CAS: -50; Tetracycline: in CAS: -88; Trimethoprim: in CAS: -11, -17, -34, -106, -2, -88, -56

Figures reproduced from Verlicchi et al. (2012)

Figure 2: Percentage removal efficiencies for (A) analgesics/NSAIDs and (B) antibiotics in WWTPs utilising CAS (o) and MBR (x) systems. Average removal values for each technology are shown at the base of each plot. Where no value is indicated, no removal data was available for that compound.

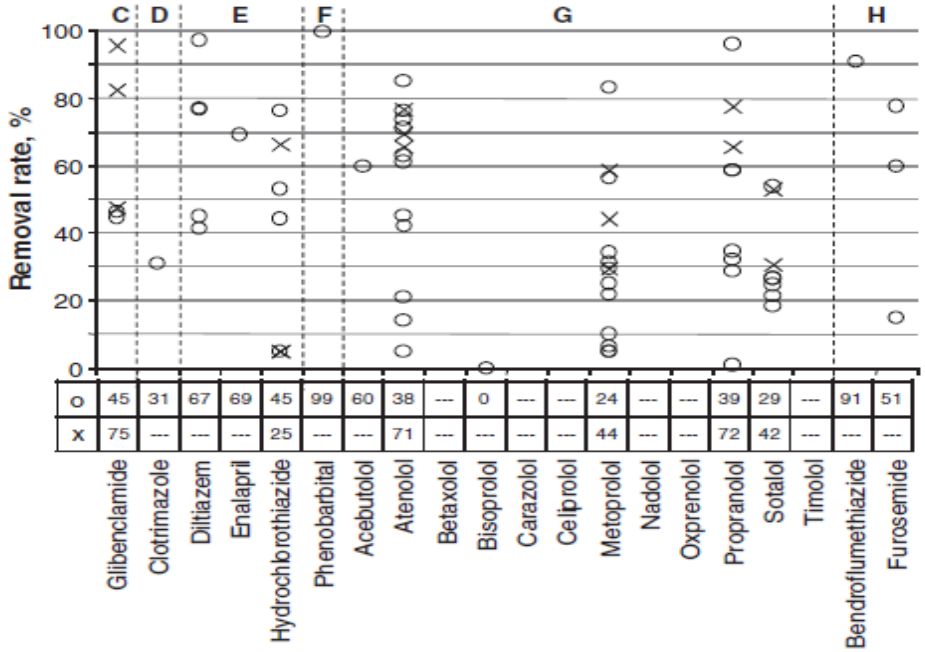
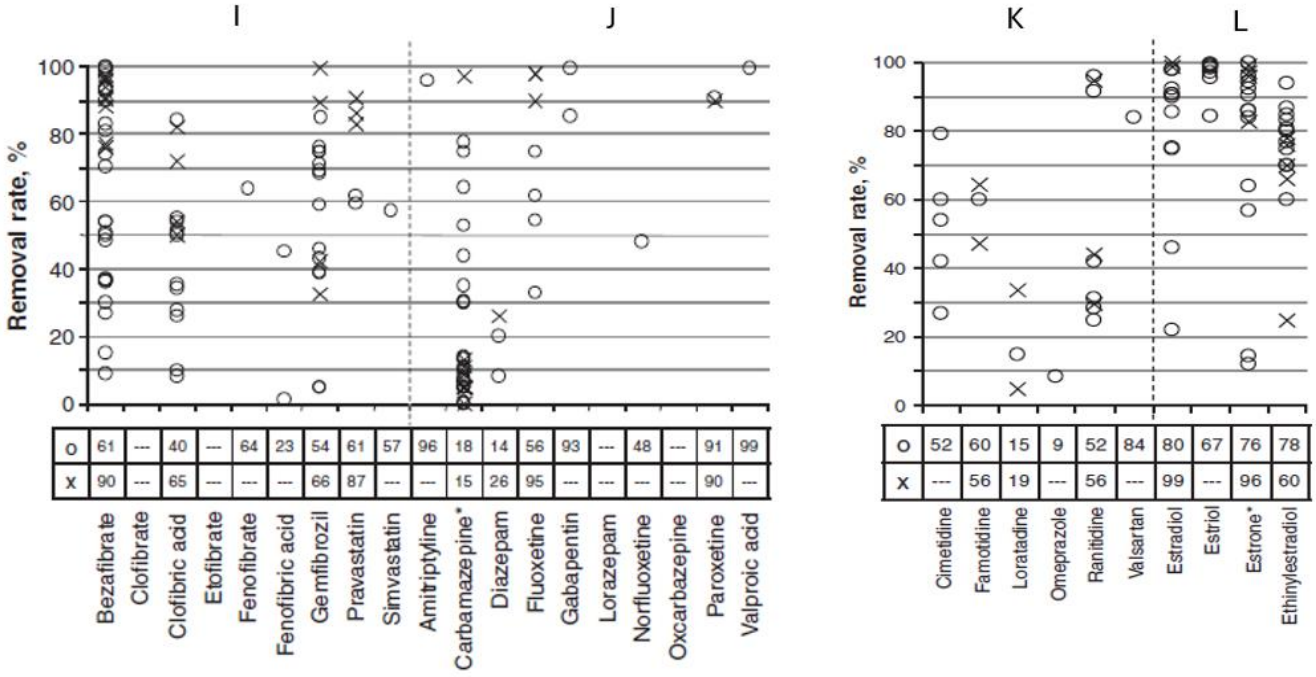


Figure reproduced from Verlicchi et al. (2012)

Figure 3: Percentage removal efficiencies for (C) anti-diabetics, (D) anti-fungals, (E) anti-hypertensives, (F) barbiturates, (G) beta blockers and (H) diuretics in WWTPs utilising CAS (o) and MBR (x) systems. Average removal values for each technology are shown at the base of each plot. Where no value is indicated, no removal data was available for that compound.



*Observed negative removal efficiencies
Carbamazepine: in CAS: -122, -3, -47, -43, -35, -4, -67, -11, -3, -43, -12. In MBR: -13
Estrone: In CAS: -112, -35, -83, -40.

Figures reproduced from Verlicchi et al. (2012)

Figure 4: Percentage removal efficiencies for (I) lipid regulators, (J) psychiatric drugs, (K) receptor agonists and (L) hormones, in WWTPs utilising CAS (o) and MBR (x) systems. Average removal values for each technology are shown at the base of each plot. Where no value is indicated, no removal data was available for that compound.

5. RISK ESTIMATION

Recreational use of aquatic environments is a favourite pastime of many New Zealanders, and a wide range of different activities bring people into contact with water that may be impacted by wastewater discharge or overflow (Cressey 2023). However, estimating the potential risk to human health posed by exposure to wastewater-borne contaminants in the environment – especially emerging contaminants such as pharmaceuticals – can be a complex task (Kositch et al. 2014). In particular, exposure assessment requires characterising the real or potential environmental occurrence of the contaminants of concern, and information on human behaviours that will result in exposure to these contaminants (Duarte et al. 2022; Cressey 2023). However, the preceding chapters have demonstrated that limited data exist on environmental concentrations for a small proportion of the range of APIs in common use, with little-to-no data for many more, especially in Aotearoa New Zealand.

Human exposure to chemicals in the aquatic environment can occur through multiple exposure routes, including direct ingestion of contaminant-containing water and dermal absorption of chemicals present in water. In order to integrate the exposure contributions from different exposure routes, an understanding of the way in which a compound will be absorbed across various body surfaces is required. Further, to be able to characterise the risks associated with the estimated exposure, an understanding of the health effects that may result for different intensities or durations of exposure is required (ie, hazard characterisation or dose response data). As discussed below, much of that data on dose-response relationships for pharmaceutical compounds is sparce or not publicly available.

Despite these challenges, the following chapter seeks to provide insights into the potential risks to human health associated with exposure to pharmaceuticals during recreational use of wastewater-impacted receiving environments. It utilises the exposure model tool developed by Cressey (2023) whereby each unique set of inputs into the model (ie, chemical of concern, environmental concentration) define an exposure scenario and a series of consequent risk estimates for several recreational activities. Noting the limitations in available data, this risk estimation can be considered a Tier 1 or screening-level risk assessment to determine whether more detailed investigation or assessments of risk are warranted.

5.1 RISK ASSESSMENT

Risk assessment or estimation is the central scientific component of risk analysis, informing the other components of risk analysis, risk management and risk communication. It aims to characterise public health risk by evaluating the levels of exposure to a substance that pose a risk of adverse health outcomes, and then comparing them with estimated levels of exposure over a specified period of time (FAO/WHO 2009). Key definitions essential to risk assessment include (IPCS 2004):

Hazard: an inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent.

Risk: the probability of an adverse effect in an organism, system or (sub)population caused under specified circumstances by exposure to an agent.

Within the scope of this report, the hazard will therefore be an inherent property of the pharmaceutical compound (ie, the agent), while the risk will depend on the context, notably the exposure route, exposure intensity, and the exposed individual(s) or population.

The chemical risk assessment or estimation process itself contains four key stages, as summarised below (IPCS 2004; FAO/WHO 2009).

Hazard identification: identification of the type and nature of adverse health effects that an agent (eg, a pharmaceutical compound) has the capacity to cause. For established/conventional contaminants, hazard identification is usually based on data from international sources and evaluates the weight of evidence for adverse health effects based on assessment of data on toxicity, epidemiology and mode of action; these studies may include observations in humans, studies in laboratory animals or *in vitro* and/or *in silico* studies.

Hazard characterisation (dose response): the evaluation of the relationship between the exposure dose of an agent and the incidence of an adverse effect, known as the dose response. Most chemicals have a dose threshold for toxicity, and for these it is usual to determine a 'no observed adverse effects level' (NOAEL) or a dose equating to a minimal effect, known as a benchmark dose (BMD). Following application of uncertainty or safety factors, health-base guidance values (HBGVs) can be derived, such as Acceptable Daily Intake or Tolerable Daily Intake (TDI). These HBGVs are then used as benchmarks to assess the potential effects of exposure to a chemical.

Exposure assessment: the qualitative and/or quantitative evaluation of the likely intake or exposure to the chemical agent. This process is highly context-dependent, with exposure being a function of the concentration of the chemical in the surrounding media (air, water, food etc) and the rate of intake of media through relevant exposure routes.

Risk characterisation: the qualitative and/or quantitative determination (including attendant uncertainties) of the probability of occurrence and severity of known and potential adverse health effects in a given (sub)population under defined exposure conditions (ie, based on hazard identification, hazard characterisation and exposure assessment).

5.1.1 Hazard identification

To determine the pharmaceutical residues or APIs that could constitute hazardous agents in the context of recreational use of aquatic environments, we selected a subset of the compounds identified in Chapter 3 that included both compounds with high concentrations in

wastewater, as well as several representative compounds from across different therapeutic classes. These compounds were as follows:

- Acetaminophen
- Diclofenac
- Ibuprofen
- Naproxen
- Salicylic acid
- Amoxicillin
- Erythromycin
- Sulfamethazine
- Sulfamethoxazole
- Trimethoprim
- Carbamazepine
- Gabapentin
- Metformin
- Diltiazem
- Valsartan
- Metoprolol
- Bezafibrate
- Gemfibrozil
- Hydrochlorothiazide
- Furosemide
- Amitriptyline
- Lorazepam
- Sertraline
- Venlafaxine
- 17β-estradiol
- Iohexol
- Pantoprazole
- Salbutamol

Pharmaceuticals are somewhat unique amongst the chemical contaminants typically considered in risk assessments, as they are usually deliberately administered to people (eg, via ingestion, inhalation, topical application etc) to elicit beneficial or therapeutic effects (Cressey 2018). As such, pharmaceuticals are governed by stringent regulatory processes and require rigorous pre-clinical and clinical studies to assess their efficacy and safety before commercial production (WHO 2012). However, all pharmaceuticals have the potential to cause adverse side effects, especially in sensitive individuals, or may be contraindicated with other pharmaceutical compounds or treatments (Stampfer et al. 2019; Sengar and Vijayananadan 2022). Purported side effects vary widely between different compounds and doses, and can range from headaches, nausea, fatigue or mild rash, to serious allergic reactions, liver or kidney injury, haematological abnormalities, endocrine disruption and hormonal effects, teratogenicity, mutagenicity and carcinogenicity[16] (Daughton and Ternes 1999; Cressey 2018; Lim et al. 2024). Thus, although the amounts of pharmaceuticals that people may be exposed to through environmental contact are likely to be very much lower than those ingested for medication, in circumstances of unintended exposure, where there is unlikely to be any benefit to the individual, the low levels of risk associated with pharmaceuticals must still be considered (Cressey 2018).

5.1.2 Hazard characterisation

A challenge of using conventional risk assessment to characterise the human health risks associated with environmental exposure to pharmaceuticals is selecting an appropriate HBGV. For most pharmaceuticals, chronic exposure to concentrations well below those producing therapeutic effects is seldom assessed[17] and the lack of comprehensive toxicological data available in the public domain means that it is seldom possible to derive a

[16] https://www.medsafe.govt.nz/consumers/Safety-of-Medicines/Medicine-safety.asp

[17] Data on low-level exposures is more likely to exist in situations where pharmaceuticals may be present as contaminants, such as veterinary medicines used in animal husbandry and food production, or where multiple pharmaceuticals are produced in a facility with the potential for cross contamination.

NOAEL or HBGV such as ADI or TDI (WHO 2012; Khan and Nicell 2015; Duarte et al. 2022), which are more appropriate to risk assessment in the context of unintended or environmental exposure. In the absence of such data, several studies have used the minimum therapeutically-effective dose (MED) for the relevant API as a proxy HBGV, for example, in assessing the human health risks associated with the presence of pharmaceutical contaminants in drinking-water (see WHO 2012). However, MED is typically determined through controlled studies that may not account for sensitivities of sub-populations who would not normally be prescribed or recommended a medication. Further, the dose sufficient to achieve a therapeutic effect may be different to the dose where adverse health effects can occur, reflecting different end points (Stampfer et al. 2019).[18] Similarly, the maximum tolerated dose (MTD) is the highest dose of a drug or treatment that achieves a desired benefit under controlled circumstances but does not cause 'unacceptable side effects' or overt toxicity, and is often determined over a relatively short period of time (eg, single dose or 24-hour period); it is therefore unlikely to be protective when considering sensitive individuals or chronic exposure.[19]

Where HBGVs for the pharmaceuticals identified in Section 5.1.1 have been established by the World Health Organization (WHO), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Food Safety Authority (EFSA), the United States Environmental Protection Agency (US EPA) or the Agency for Toxic Substances and Disease Registry (ATSDR), these values were used in the model to inform the risk characterisation.[20] Where no established HBGV was available, the threshold of toxicological concern (TTC) approach was used. Threshold of toxicological concern is a pragmatic and conservative screening and prioritisation tool that has been used to assess the safety of substances in food, water, cosmetics and pharmaceuticals, where the chemical structure of the substance is known and human exposure to it can be estimated, but where there is limited chemical-specific toxicity data available (EFSA 2019). Briefly, the concept is based on the Cramer classification scheme, where a series of sequential questions forms a decision tree, assigning a compound to one of three classes based on its structural characteristics (eg structure complexity, functional groups etc) and knowledge of the toxicity and metabolism of those chemical structures by mammalian metabolic pathways. Each class is associated with a TTC value that describes a conservative generic human chronic exposure threshold derived from a database of various chemicals for which good toxicological data exists, before applying uncertainty and safety factors. The TTC value is a level of daily oral exposure to a chemical over a lifetime that is considered to be of no appreciable risk to human health. If the exposure to the chemical of concern is below the relevant TTC value for the Cramer Class to which it was assigned, the probability that it would cause adverse health effects is low. If the estimated exposure to a substance is higher than the relevant TTC value, a non-TTC approach is required to reach conclusions as to potential adverse health effects. TTC values for Cramer Classes I, II and III are 30, 9 and 1.5 µg per kilogram of body weight per day, respectively. Separate TTC values are set for particular neurotoxicants (organophosphates and carbamates) and compounds that are potentially DNA-reactive mutagens and/or carcinogens. None of the pharmaceuticals assessed were likely to belong to these chemical classes. The TTC approach is not

[18] For example, adverse side effects may occur at or below minimum therapeutic doses, but may be considered acceptable when compared to the benefits afforded by the drug.

[19] https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/maximum-tolerated-dose

[20] Specifically, a search was made of the following collections: US EPA Reference Dose; CDC/ATSDR Minimum Risk Level; JECFA ADI/TDI or provisional tolerable intakes; US EPA Drinking-water Contaminant Limits; and WHO Drinking-Water Guidelines.

appropriate for assessing exposure to steroids. Additional information on the TTC approach can be found in guidance documentation produced by the European Food Safety Authority (EFSA 2019). We utilised Toxtree[21], a computer-based implementation of the Cramer scheme to classify pharmaceutical compounds so a TTC value could be assigned.

The HBGVs for pharmaceuticals used in the risk estimation are shown in Table 10.

Table 10: Health-based guidance values for pharmaceuticals used in the risk estimation.

Therapeutic class	Pharmaceutical compound	HBGV (mg / kg bw / day)	Basis for HBGV
Analgesic/NSAIDs	Acetaminophen	0.03	TTC Cramer Class I
Analgesic/NSAIDs	Diclofenac	0.0015	TTC Cramer Class III
Analgesic/NSAIDs	Ibuprofen	0.03	TTC Cramer Class I
Analgesic/NSAIDs	Naproxen	0.0015	TTC Cramer Class III
Analgesic/NSAIDs	Salicylic acid	0.03	TTC Cramer Class I
Antibiotics	Amoxicillin	0.002	JECFA ADI
Antibiotics	Erythromycin	0.0007	JECFA ADI
Antibiotics	Sulfamethazine	0.05	JECFA ADI
Antibiotics	Sulfamethoxazole	0.0015	TTC Cramer Class III
Antibiotics	Trimethoprim	0.0015	TTC Cramer Class III
Anti-asthmatics	Salbutamol	0.03	TTC Cramer Class I
Anti-epileptics	Carbamazepine	0.0015	TTC Cramer Class III
Anti-epileptics	Gabapentin	0.0015	TTC Cramer Class III
Anti-diabetics	Metformin	0.0015	TTC Cramer Class III
Anti-hypertensives	Diltiazem	0.0015	TTC Cramer Class III
Anti-hypertensives	Valsartan	0.0015	TTC Cramer Class III
Beta blockers	Metoprolol	0.0015	TTC Cramer Class III
Blood lipid regulators	Bezafibrate	0.0015	TTC Cramer Class III
Blood lipid regulators	Gemfibrozil	0.03	TTC Cramer Class I
Diuretics	Hydrochlorothiazide	0.0015	TTC Cramer Class III
Diuretics	Furosemide	0.0015	TTC Cramer Class III
Psychiatric drugs	Amitriptyline	0.0015	TTC Cramer Class III
Psychiatric drugs	Lorazepam	0.0015	TTC Cramer Class III
Psychiatric drugs	Sertraline	0.0015	TTC Cramer Class III
Psychiatric drugs	Venlafaxine	0.03	TTC Cramer Class I
Steroid hormones	17B-estradiol	0.00005	JECFA ADI
X-ray contrasts	Iohexol	0.0015	TTC Cramer Class III
Other	Pantoprazole	0.0015	TTC Cramer Class III

bw – body weight

[21] https://apps.ideaconsult.net/data/ui/toxtree#

5.1.3 Exposure assessment

Routes of exposure

A wide range of recreational activities bring New Zealanders into contact with water that is potentially impacted by wastewater discharge or overflow. These activities may be classified into three tiers according to the extent of contact (WHO 2021):

- Primary or whole-body contact recreation. Activities during which the participant is intentionally in contact with the water, the trunk and face are frequently submerged or splashed, and where it is likely that some water will be swallowed.
- Secondary or incidental contact recreation. Activities during which only parts of the body (ie, limbs) may regularly come into contact with the water, and swallowing water is unusual.
- Non-contact recreation. Activities that occur in proximity to waterways, but where contact with water is not intentional, such as sunbathing or walking adjacent to waterways.

Individuals engaging in recreational activities where waterways are impacted by wastewater discharge are therefore potentially exposed to associated chemical contaminants through oral, dermal and/or inhalation routes.[22]

The model developed by Cressey (2023) calculates exposure and associated risk estimates for each of several recreational activities: swimming (primary contact), surfing (primary contact), rowing (secondary contact), canoeing/kayaking (secondary contact), sailing (secondary contact), fishing (secondary contact). The model considers the frequency and duration of each activity, as well as the extent to which the different routes of exposure (ie, oral, dermal, inhalation) are associated each activity; for example, for swimming, it considers how much water is likely ingested during each event, and how much of the body surface is in contact with the water and for what proportion of the swimming event. Inhalation is not included in the model due to a lack of available data as to how much water or aerosol might be inhaled during the various activities, and the rationale that it was likely to be a minor exposure route for most activities when compared to ingestion and/or dermal contact.

Exposure can be estimated as an external dose (the amount of the chemical meeting the surface of the body) or as an internal dose (the amount of the chemical that is absorbed from the gut, lung of skin into the portal circulation). To assess exposure by multiple routes, exposures need to be converted to a common basis. As most HBGVs are defined in terms of oral exposure (external dose), dermal exposures are usually determined initially as an internal dose, and then converted to an oral equivalent dose. This process requires knowledge of the rates of dermal and oral absorption for the chemical or applicable substitute assumptions. The model includes the ability to enter data (where it exists) on the oral absorption rate or dermal permeability coefficient, to improve estimates of the extent to which the chemical is likely to be absorbed across the gut or skin, respectively. In the absence of this information, a conservative approach was taken in assuming that the API

[22] Oral exposure relates to the ingestion of solids or liquids with subsequent absorption of compounds across the gastrointestinal tract; inhalation exposure relates to absorption that occurs across the lining of the lungs, and dermal exposure relates to absorption of compounds through the skin or mucosal membranes, such as those in the nose or eyes.

would be completely absorbed from the gastrointestinal tract. Similarly, in the absence of available information regarding the dermal absorption of the selected pharmaceuticals, the model estimates dermal absorption based on the physical properties of the compound (molecular weight, water-octanol solubility coefficient). Knowledge of the rate of oral absorption or an assumption of complete absorption allows the dermally absorbed dose to be converted to an oral equivalent exposure dose, such that total oral exposure can be estimated for comparison with the respective oral HBGV (Cressey 2023).

Detailed explanations as to the derivation of model parameters defining potential exposure routes are provided in Cressey (2023).

The model does not consider exposure to wastewater-borne contaminants through the following routes, thus these are not included in the current risk estimation:

- consumption of aquatic organisms (eg shellfish) that are contaminated as a result of wastewater discharges, or
- consumption of drinking-water that becomes contaminated by wastewater, for example through leaching of land-applied effluents to groundwater, or discharge to freshwater used as drinking-water sources.

Environmental concentration

Since the exposure model considers only exposures relating to recreational use of contaminated aquatic environments, only the data on pharmaceutical concentrations in wastewater and surface and marine waters is considered; sediments, biowastes, groundwater and drinking-waters are excluded. Mean wastewater concentrations for those compounds listed in the hazard identification were collated from New Zealand data on treated wastewater compiled in Chapter 3. Since HBGVs are usually intended for assessing chronic exposures to environmental contaminants, mean values were used in preference to maximum values as a better representation of the concentrations one might experience over a longer period of time[23]. Where several studies reported mean values, the higher of these values was selected as the more conservative approach. A small number of pharmaceuticals detected in international studies were also included to enable assessment across a more diverse range of compounds; in these cases (which are indicated in Table 11), the highest mean value reported for the compound in treated effluents was used, as per the approach for New Zealand data.

The concentration of a chemical contaminant in a wastewater-impacted environment (and therefore experienced by recreational users of that environment) will be a function of the contaminant's concentration in wastewater, the dilution by the receiving environment, and the degradation in the environment between the time of the discharge and the time of exposure. Information on degradation is not normally available and it is generally assumed that the degradation will not be significant (Cressey 2023). Dilution is dictated by the hydrodynamics of the particular recreational situation and setting, and cannot be modelled generically; while the model does include the capacity to consider dilution factors where these are known for a specific situation, in the absence of that information or in applying the model to a generic scenario such as the present assessment, an assumption of negligible

[23] Noting however that most of the New Zealand data sets included only a very small number – or even single – samples.

dilution allows for an appropriately conservative approach (Cressey 2023). The concentrations determined for wastewater were therefore used as a proxy for environmental concentration. The concentrations assessed for each pharmaceutical are shown in Table 11.

5.1.4 Risk characterisation

Table 11 summarises the risk characterisation for exposure to pharmaceuticals occurring through various recreational activities being undertaken in wastewater-impacted waters. The estimation is inherently conservative, in assuming recreation occurs at the site of wastewater discharge, with no dilution by the receiving environment, and that all of the pharmaceutical dose ingested will be absorbed across the gastrointestinal tract. For each pharmaceutical assessed, the estimated exposure associated with each activity was characterised as a risk index, calculated as the exposure as a proportion of the respective HBGV. Where a risk index is less than 1 (ie, the exposure is less than the HBGV), the exposure is considered acceptable or tolerable; the further the estimate is below the HBGV, the smaller the risk index and the lower the risk.

Estimates of exposure to the selected pharmaceuticals were well below HBGVs, in most cases by several orders of magnitude, with the risk index seldom exceeding 0.002. The highest single risk index was calculated for exposure to metformin when surfing; despite the environmental concentration used (200,000 ng/L) likely being overestimated, the risk index was still below 1, at 0.347. Taken together, the data suggest that there is no appreciable risk to people's health from exposure to pharmaceuticals during the recreational activities considered herein. However, it should be noted that risks were assessed based on exposure to individual pharmaceuticals, rather than concurrent exposure to multiple compounds, as is more likely to occur with environmental exposure. At this time, there is no agreed approach as to how exposure to complex pharmaceutical mixtures should be assessed, as it requires a detailed understanding of the interactions between the various compounds present and their potential to cause additive, synergistic or antagonistic effects (Duarte et al. 2022; Bloch et al. 2023; P. Cressey, personal communication, July 2024). The development of approaches and tools for harmonising the assessment of risk from chemical mixtures is an active area of research.[24]

The current risk estimation should be considered a screening assessment only. While it does not suggest that further investigation is urgently required from a human health perspective, it does not preclude further risk assessment in the future, for example, if new information becomes available prompting revision of HBGVs or information on environmental presence of pharmaceuticals that differs from that described here. Similarly, this risk estimation does not exclude the potential risks associated with exposure to pharmaceuticals through routes not covered in this assessment (eg, shellfish, drinking-water) or potential risks to ecological health.

[24] https://www.efsa.europa.eu/en/topics/topic/chemical-mixtures

Table 11: Summary of risk estimation parameters, including estimated total exposure and associated risk index (shown below exposure, as a proportion of the associated HBGV) for selected pharmaceuticals detected in New Zealand municipal wastewater effluents, during a Tier 1 assessment.

Pharmaceutical	Wastewater effluent concentration (ng/L)	HBGV (mg/kg/day)	Total exposure (mg/kg bw/day) and risk index								
			Swimming (FW, child)	Swimming (FW, adult)	Swimming (M, child)	Swimming (M, adult)	Surfing	Canoeing/ kayaking	Rowing	Sailing	Fishing
Acetaminophen	82,000	0.03	2.6×10^{-5} 0.001	1.9×10^{-6} <0.001	3.2×10^{-5} 0.001	2.1×10^{-6} <0.001	2.2×10^{-4} 0.007	2.7×10^{-6} <0.001	3.4×10^{-6} <0.001	1.1×10^{-5} <0.001	1.8×10^{-6} <0.001
Diclofenac	1,000	0.0015	1.1×10^{-5} 0.007	3.1×10^{-6} 0.002	1.2×10^{-5} 0.008	3.3×10^{-6} 0.002	2.1×10^{-5} 0.014	1.1×10^{-6} 0.001	3.3×10^{-6} 0.002	1.8×10^{-5} 0.012	7.7×10^{-7} 0.001
Ibuprofen	8,700	0.03	7.0×10^{-5} 0.002	2.0×10^{-5} 0.001	7.8×10^{-5} 0.003	2.2×10^{-5} 0.001	1.4×10^{-4} 0.005	7.3×10^{-6} <0.001	2.1×10^{-5} 0.001	1.2×10^{-4} 0.004	5.1×10^{-6} <0.001
Naproxen	2,200	0.0015	5.1×10^{-6} 0.003	1.3×10^{-6} 0.001	5.7×10^{-6} 0.004	1.4×10^{-6} 0.001	1.3×10^{-5} 0.009	5.3×10^{-7} <0.001	1.4×10^{-6} 0.001	7.8×10^{-6} 0.005	3.6×10^{-7} <0.001
Salicylic acid	7,400	0.03	8.6×10^{-6} 0.000	1.9×10^{-6} <0.001	9.8×10^{-6} <0.001	2.1×10^{-6} <0.001	3.0×10^{-5} 0.001	8.9×10^{-7} <0.001	2.5×10^{-6} <0.001	1.5×10^{-5} <0.001	7.0×10^{-7} <0.001
Amoxicillin*	1,700	0.002	5.1×10^{-7} <0.001	2.8×10^{-8} <0.001	6.1×10^{-7} <0.001	3.1×10^{-8} <0.001	4.5×10^{-6} 0.002	5.2×10^{-8} <0.001	5.4×10^{-8} <0.001	1.2×10^{-7} <0.001	3.2×10^{-8} <0.001
Erythromycin*	1,400	0.0007	5.0×10^{-7} 0.001	4.8×10^{-8} <0.001	6.0×10^{-7} 0.001	5.2×10^{-8} <0.001	3.9×10^{-6} 0.006	5.2×10^{-8} <0.001	7.1×10^{-8} <0.001	2.5×10^{-7} <0.001	3.3×10^{-8} <0.001
Sulfamethazine	12	0.05	3.4×10^{-9} <0.001	1.5×10^{-10} <0.001	4.2×10^{-9} <0.001	1.7×10^{-10} <0.001	3.2×10^{-8} <0.001	3.5×10^{-10} <0.001	3.3×10^{-10} <0.001	5.9×10^{-10} <0.001	2.2×10^{-10} <0.001
Sulfamethoxazole	1,700	0.0015	5.5×10^{-7} <0.001	4.1×10^{-8} <0.001	6.7×10^{-7} <0.001	4.6×10^{-8} <0.001	4.6×10^{-6} 0.003	5.7×10^{-8} <0.001	6.8×10^{-8} <0.001	2.0×10^{-7} <0.001	3.5×10^{-8} <0.001
Trimethoprim	570	0.0015	1.8×10^{-7} <0.001	1.2×10^{-8} <0.001	2.2×10^{-7} <0.001	1.4×10^{-8} <0.001	1.5×10^{-6} 0.001	1.8×10^{-8} <0.001	2.1×10^{-8} <0.001	5.8×10^{-8} <0.001	1.2×10^{-8} <0.001
Carbamazepine	1,100	0.0015	1.0×10^{-6} 0.001	2.2×10^{-7} <0.001	1.2×10^{-6} 0.001	2.4×10^{-7} <0.001	4.1×10^{-6} 0.003	1.0×10^{-7} <0.001	2.5×10^{-7} <0.001	1.3×10^{-6} 0.001	7.0×10^{-8} <0.001
Gabapentin	26,000	0.0015	7.2×10^{-6} 0.005	2.5×10^{-7} <0.001	8.7×10^{-6} 0.006	2.9×10^{-7} <0.001	6.8×10^{-5} 0.045	7.3×10^{-7} <0.001	6.4×10^{-7} <0.001	8.2×10^{-7} 0.001	4.5×10^{-7} <0.001
Metformin	200,000	0.0015	5.4×10^{-5} 0.036	1.6×10^{-6} 0.001	6.6×10^{-5} 0.044	1.9×10^{-6} 0.001	5.2×10^{-2} 0.347	5.5×10^{-6} 0.004	4.6×10^{-6} 0.003	4.6×10^{-6} 0.003	3.4×10^{-6} 0.002
Diltiazem	370	0.0015	2.2×10^{-7} <0.001	3.9×10^{-8} <0.001	2.6×10^{-7} <0.001	4.3×10^{-8} <0.001	1.2×10^{-6} 0.001	2.3×10^{-8} <0.001	4.7×10^{-8} <0.001	2.2×10^{-7} <0.001	1.5×10^{-8} <0.001

Table 11 continued. Summary of risk estimation parameters, including estimated total exposure and associated risk index (shown below exposure, as a proportion of the associated HBGV) for selected pharmaceuticals detected in New Zealand municipal wastewater effluents, during a Tier 1 assessment.

Pharmaceutical	Wastewater effluent concentration (ng/L)	HBGV (mg/kg/day)	Total exposure (mg/kg bw/day) and risk index								
			Swimming (FW, child)	Swimming (FW, adult)	Swimming (M, child)	Swimming (M, adult)	Surfing	Canoeing/ kayaking	Rowing	Sailing	Fishing
Valsartan*	1,600	0.0015	3.8×10^{-6} 0.003	1.0×10^{-6} 0.001	4.3×10^{-6} 0.003	1.1×10^{-6} 0.001	8.1×10^{-7} 0.001	4.7×10^{-8} <0.001	1.4×10^{-7} <0.001	7.7×10^{-7} 0.001	3.2×10^{-8} <0.001
Metoprolol	3,100	0.0015	1.5×10^{-6} 0.001	2.3×10^{-7} <0.001	1.8×10^{-6} 0.001	2.5×10^{-7} <0.001	9.3×10^{-6} 0.006	1.6×10^{-7} <0.001	2.9×10^{-7} <0.001	1.3×10^{-6} 0.001	1.0×10^{-7} <0.001
Bezafibrate*	230	0.0015	8.0×10^{-7} 0.001	2.2×10^{-7} <0.001	8.9×10^{-7} 0.001	2.4×10^{-7} <0.001	1.9×10^{-6} 0.001	8.4×10^{-8} <0.001	2.3×10^{-7} <0.001	1.3×10^{-6} 0.001	5.8×10^{-8} <0.001
Gemfibrozil*	240	0.03	1.2×10^{-5} <0.001	3.4×10^{-6} <0.001	1.3×10^{-5} <0.001	3.6×10^{-6} <0.001	2.1×10^{-5} 0.001	1.2×10^{-6} <0.001	3.6×10^{-6} <0.001	2.0×10^{-5} 0.001	8.4×10^{-7} <0.001
Hydrochlorothiazide	600	0.0015	1.7×10^{-7} <0.001	6.7×10^{-9} <0.001	2.1×10^{-7} <0.001	7.6×10^{-9} <0.001	1.6×10^{-6} 0.001	1.7×10^{-8} <0.001	1.6×10^{-8} <0.001	2.4×10^{-8} <0.001	1.1×10^{-8} <0.001
Furosemide	310	0.0015	1.4×10^{-7} <0.001	2.0×10^{-8} <0.001	1.7×10^{-7} <0.001	2.2×10^{-8} <0.001	9.1×10^{-7} 0.001	1.5×10^{-8} <0.001	2.6×10^{-8} <0.001	1.1×10^{-7} <0.001	9.7×10^{-9} <0.001
Amitriptyline*	30	0.0015	5.6×10^{-8} <0.001	1.4×10^{-8} <0.001	6.3×10^{-8} <0.001	1.5×10^{-8} <0.001	1.6×10^{-7} <0.001	5.8×10^{-9} <0.001	1.5×10^{-8} <0.001	8.3×10^{-8} <0.001	4.0×10^{-9} <0.001
Lorazepam*	40	0.0015	2.5×10^{-8} <0.001	4.6×10^{-9} <0.001	2.9×10^{-8} <0.001	5.0×10^{-9} <0.001	1.3×10^{-7} <0.001	2.6×10^{-9} <0.001	5.4×10^{-9} <0.001	2.6×10^{-8} <0.001	1.7×10^{-9} <0.001
Sertraline*	21	0.0015	4.5×10^{-7} <0.001	1.3×10^{-7} <0.001	4.9×10^{-7} <0.001	1.4×10^{-7} <0.001	8.1×10^{-7} 0.001	4.7×10^{-8} <0.001	1.4×10^{-7} <0.001	7.7×10^{-7} 0.001	3.2×10^{-8} <0.001
Venlafaxine	1,200	0.03	2.2×10^{-6} <0.001	5.7×10^{-7} <0.001	2.5×10^{-6} <0.001	6.2×10^{-7} <0.001	6.4×10^{-6} <0.001	2.3×10^{-7} <0.001	6.2×10^{-7} <0.001	3.3×10^{-6} <0.001	1.6×10^{-7} <0.001
17β-estradiol	19	0.00005	1.1×10^{-7} 0.002	3.1×10^{-8} 0.001	1.2×10^{-7} 0.002	3.4×10^{-8} 0.001	2.3×10^{-7} 0.005	1.2×10^{-8} <0.001	3.3×10^{-8} 0.001	1.9×10^{-7} 0.004	8.0×10^{-9} <0.001
Iohexol*	9,300	0.0015	2.5×10^{-6} 0.002	7.6×10^{-8} <0.001	3.1×10^{-6} 0.002	8.9×10^{-8} <0.001	2.4×10^{-5} 0.016	2.6×10^{-7} <0.001	2.1×10^{-7} <0.001	2.1×10^{-7} <0.001	1.6×10^{-7} <0.001
Pantoprazole*	130	0.0015	6.0×10^{-8} <0.001	8.2×10^{-9} <0.001	7.0×10^{-8} <0.001	8.9×10^{-9} <0.001	3.8×10^{-7} <0.001	6.1×10^{-9} <0.001	1.1×10^{-8} <0.001	4.5×10^{-8} <0.001	4.0×10^{-9} <0.001
Salbutamol	63	0.03	2.5×10^{-8} <0.001	2.9×10^{-9} <0.001	3.0×10^{-8} <0.001	3.2×10^{-9} <0.001	1.8×10^{-7} <0.001	2.6×10^{-9} <0.001	4.0×10^{-9} <0.001	1.6×10^{-8} <0.001	1.7×10^{-9} <0.001

*Data from international study; no NZ data was available. FW – freshwater; M – marine.

6. CONCLUSIONS

Pharmaceuticals are increasingly being reported as environmental contaminants, raising concerns as to their potential risks to human and environmental health. Municipal wastewater is the primary source of pharmaceuticals to the environment, with unmetabolised parent compounds and/or bioactive metabolites excreted in patient urine and/or faeces. The presence of specific pharmaceuticals and their relative concentration generally reflects their usage within the catchment community. In New Zealand, the most highly-dispensed pharmaceuticals include various analgesics, NSAIDs, antibiotics, blood lipid regulators, anti-depressants and other psychiatric medications, anti-hypertensives, anti-asthmatics, beta blockers, diuretics, antihistamines, and diabetes medications.

Relatively little data was available on the presence of pharmaceuticals in wastewater in Aotearoa New Zealand, most of which focused on a small number of pharmaceutical analytes from a small number of samples (often one or two samples from a single WWTP). The available data determined that 57 different pharmaceuticals (including 2 metabolites) have been detected in wastewaters, and of these, 23 are among the 100 most highly-dispensed pharmaceuticals in New Zealand. Although likely biased by their prevalence in analytical suites, the most-commonly detected pharmaceuticals were acetaminophen, diclofenac, ibuprofen, naproxen, sulfamethoxazole, trimethoprim, carbamazepine and diltiazem. Where quantifiable levels of pharmaceuticals were detected, concentrations ranged from several ng/L to tens of µg/L; in most cases, concentrations tended towards tens to hundreds of ng/L. A further 32 pharmaceuticals were inferred as being present in New Zealand wastewater, by virtue of their presence in environmental samples, where the most plausible explanation for their presence was wastewater-related contamination. Overall, the available data on pharmaceuticals in wastewater in Aotearoa New Zealand are consistent with reports from overseas, both in terms of the types and quantities of compounds identified; it would seem reasonable, therefore, that many of the additional pharmaceuticals detected in international studies may also be present to some extent in New Zealand wastewaters. There is insufficient data available to draw conclusions as to New Zealand-specific trends around seasonal presence or the roles of local factors that may influence the presence and/or removal of compounds, such as the size or demographics of a community served by a given WWTP, local climate or the treatment processes and operating parameters of the treatment plant.

Only two studies were identified in which the removal of pharmaceuticals from wastewater were investigated; both studies involved WWTP utilising activated sludge systems, with one also treating ~25% of wastewater by MBR. Ibuprofen, salicylic acid, 17α-ethinylestradiol, acetaminophen, naproxen, clarithromycin and roxithromycin were relatively well removed (ie, approximately >85%), with moderate removal rates for diltiazem, sulfamethoxazole, fluoxetine and atenolol (ie >60%). Diclofenac, trimethoprim and metoprolol were poorly removed (<35%), with carbamazepine showing almost no removal.

A Tier 1 screening-level assessment to estimate the potential human health risks associated with exposure to 28 representative pharmaceuticals during recreational use of wastewater-impacted environments indicated that exposures were below their respective health-based guidance values by several orders of magnitude. These findings indicate that there is no appreciable risk to people's health as a result of possible exposure to pharmaceuticals during swimming, surfing canoeing/kayaking, rowing, sailing or fishing. The assessment

does not include exposures resulting from contaminated drinking-water or mahinga kai. Given the dearth of publicly available toxicological data for most pharmaceuticals and the lack of studies assessing the effects of chronic exposure to sub-therapeutic levels, the assumptions of the assessment were set conservatively. However, it should be noted that risks were assessed based on exposure to individual pharmaceuticals, rather than concurrent exposure to multiple compounds, as is more likely to occur with environmental exposure; at this point in time, there is no agreed approach as to how exposure to pharmaceutical mixtures should be assessed.

Like many emerging contaminants, the question of impacts on human and ecological health associated with the environmental presence of pharmaceuticals is an area of growing interest and active research. As municipal wastewater is the primary source of pharmaceuticals to the environment, characterising their presence in, and removal from, wastewater is a key part of understanding their potential environmental impacts, as well as possible solutions where required. Although based on a relatively small dataset, the current assessment suggests that further work to characterise the human health risk to recreational water users would be a low priority. Further, while not assessed here, international studies have indicated that the risks from pharmaceuticals in drinking-water are also low. However, it will be important to remain up-to-date with advances in our understanding of risk, such as developments in assessing exposure to complex pharmaceutical (or wider EOC) mixtures. The current assessment is not applicable to risks to ecological health and aquatic organisms, which are assessed against different threshold values.

APPENDIX A: PHARMACEUTICAL USE IN NEW ZEALAND – PHARMAC DATA

Data on the dispensing of pharmaceuticals in New Zealand can be collated from several sources. In this instance, we elected to use the Health NZ Pharmaceutical Web Tool as our primary source of dispensing data, because it provided greater access to raw data that provided a larger data set, which could then be filtered and sorted for further interrogation. Information on pharmaceutical dispensing is also available through the Pharmac website. The data differs somewhat between the two sources, due to minor differences in the criterion for inclusion/exclusion, and the use of calendar years or financial years. Overall, the data is consistent in terms of the pharmaceuticals that feature as those being most-widely prescribed as funded medications in New Zealand.

The Pharmaceutical Management Agency, better known as Pharmac, manages the funding that the New Zealand Government has allocated for pharmaceuticals, known as the Combined Pharmaceutical Budget (CPB). In the 2018-2019 financial year, the CPB was $985 million and funded 47.2 million prescriptions. The 100 most widely-dispensed pharmaceuticals in New Zealand for that period, as determined by the number of dispensings, are listed in Table A.1. Additional data, including the 20 most widely-prescribed pharmaceuticals and their number of dispensings between 1 July 2018 and 30 June 2022, is presented in Table A.2. As per the data in the Pharmaceutical Web Tool, only data for Pharmac-funded prescription medications dispended to individuals through a community pharmacy are included; those purchased as over-the-counter medications, administered in hospitals, or privately funded medications (eg, not government funded or individual does is ineligible for subsidies) are not included.

Table A.1: Top 100 dispensed pharmaceuticals in New Zealand, as determined by the number of dispensings, for the period 1 July 2018 to 30 June 2019.

Rank	Pharmaceutical compound	Rank	Pharmaceutical compound
1	Paracetamol	41	Chloramphenicol
2	Atorvastatin	42	Hydrocortisone butyrate
3	Omeprazole	43	Fluoxetine hydrochloride
4	Amoxicillin	44	Losartan potassium
5	Aspirin	45	Bendroflumethiazide
6	Ibuprofen	46	Ondansetron
7	Metoprolol succinate	47	Ethinyloestradiol with levonorgestrel
8	Salbutamol	48	Cilazapril with hydrochlorothiazide
9	Cilazapril	49	Fluticasone
10	Colecalciferol	50	Dabigatran
11	Prednisone	51	Hydrocortisone
12	Amoxicillin with clavulanic acid	52	Pantoprazole
13	Metformin hydrochloride	53	Folic acid
14	Levothyroxine	54	Venlafaxine
15	Zopiclone	55	Cefalexin
16	Loratadine	56	Diltiazem hydrochloride
17	Cetirizine hydrochloride	57	Lactulose
18	Codeine phosphate	58	Hydrocortisone with miconazole
19	Docusate sodium with sennosides	59	Morphine sulphate
20	Fluticasone propionate	60	Naproxen
21	Felodipine	61	Budesonide with eformoterol
22	Flucloxacillin	62	Gabapentin
23	Tramadol hydrochloride	63	Lorazepam
24	Amlodipine	64	Warfarin sodium
25	Simvastatin	65	Sertraline
26	Allopurinol	66	Escitalopram
27	Diclofenac sodium	67	Roxithromycin
28	Furosemide	68	Sodium fusidate
29	Citalopram hydrobromide	69	Nicotine
30	Quinapril	70	Clotrimazole
31	Blood glucose diagnostic test strip	71	Trimethoprim
32	Candesartan cilexetil	72	Nortriptyline hydrochloride
33	Paracetamol with codeine	73	Insulin glargine
34	Celecoxib	74	Gliclazide
35	Cetomacrogol with glycerol	75	Trimethoprim with sulphamethoxazole
36	Amitriptyline	76	Bisoprolol fumarate
37	Quetiapine	77	Clopidogrel
38	Doxycycline	78	Hydrocortisone with natamycin and neomycin
39	Doxazosin	79	Oestriol
40	Fluticasone with salmeterol	80	Erythromycin ethyl succinate

Table A.1 continued. Top 100 dispensed pharmaceuticals in New Zealand, as determined by the number of dispensings, for the period 1 July 2018 to 30 June 2019.

Rank	Pharmaceutical compound	Rank	Pharmaceutical compound
81	Vitamins	91	Diazepam
82	Loperamide hydrochloride	92	Ranitidine
83	Metronidazole	93	Potassium iodate
84	Insulin pen needles	94	Ferrous sulphate
85	Hydrogen peroxide	95	Metoclopramide hydrochloride
86	Methylphenidate hydrochloride	96	Fluticasone furoate with vilanterol
87	Ferrous fumarate	97	Clonazepam
88	Hydroxocobalamin	98	Sodium valproate
89	Orphenadrine citrate	99	Betamethasone valerate
90	Clobetasol propionate	100	Methylphenidate hydrochloride

Data obtained from https://pharmac.govt.nz/news-and-resources/official-information-act/official-information-act-responses/oia-response-new-zealand-pharmaceutical-market

Table A.2: Top 20 dispensed pharmaceuticals in New Zealand, as determined by the number of dispensings, for the period 1 July 2018 to 30 June 2022, divided into financial years.

Pharmaceutical compound	Therapeutic group	Total number of dispensings			
		2021-2022	2020-2021	2019-2020	2018-2019
Paracetamol	Analgesics	3,110,000	2,870,000	2,880,000	2,940,000
Atorvastin	Cardiovascular	1,750,000	1,640,000	1,530,000	1,430,000
Omeprazole	Alimentary	1,640,000	1,590,000	1,480,000	1,410,000
Aspirin	Antithrombotic	1,120,000	1,130,000	1,140,000	1,180,000
Ibuprofen	Analgesics	1,080,000	1,000,000	1,030,000	1,120,000
Colecalciferol	Musculoskeletal	1,050,000	950,000	840,000	790,000
Metoprolol succinate	Cardiovascular	940,000	960,000	950,000	950,000
Amoxicillin	Anti infectives	920,000	890,000	1,040,000	1,210,000
Salbutamol	Respiratory	830,000	780,000	940,000	930,000
Levothyroxine	Hormones	690,000	670,000	640,000	610,000
Cilazapril	Cardiovascular	640,000	600,000	840,000	830,000
Prednisone	Hormones	630,000	610,000	670,000	690,000
Cetirizine hydrochloride	Antihistamines	620,000	600,000	560,000	
Amlodipine	Cardiovascular	620,000	560,000		
Zopiclone	Nervous System	610,000	600,000	590,000	590,000
Docusate sodium with sennosides	Laxatives	570,000	570,000		490,000
Metformin hydrochloride	Diabetes	560,000	590,000	610,000	620,000
Loratadine	Antihistamines	540,000	560,000	560,000	570,000
Candesartan cilexitil	Cardiovascular	530,000			
Codeine phosphate	Analgesics	530,000	530,000	510,000	510,000
Amoxicillin clavulanic acid	Anti infectives		540,000	560,000	630,000
Fluticasone propionate	Respiratory			510,000	480,000

Data collated from Pharmac "Year in Review" reports available online:
https://pharmac.govt.nz/news-and-resources/order-publications/year-in-review/top-20s-for-202122/community-medicines
https://pharmac.govt.nz/assets/images/YIR-2021/Year-in-Review-2021.pdf
https://pharmac.govt.nz/assets/Uploads/2020-Year-in-Review.pdf
https://pharmac.govt.nz/assets/Year-in-Review-2018-19.pdf

APPENDIX B: DETECTION OF PHARMACEUTICALS IN NEW ZEALAND BIOSOLIDS AND ENVIRONMENTAL MATRICES

The detection of pharmaceuticals in sewage sludge, biosolids and various environmental matrices can be used to infer the presence of those compounds in wastewater, since it is often the only explanation for their environmental presence. This can be helpful in building our understanding of the presence and fate of pharmaceuticals in wastewater in Aotearoa New Zealand, given the small and fragmented datasets that exist currently. New Zealand-based studies on the presence of pharmaceuticals in sludge, biosolids, marine and freshwater environments (both water and sediments) and groundwaters are limited, and have been described within the main report. Tables B.1 to B.4 below provide additional detail as to the concentrations that were reported.

Table B.1: Concentrations of pharmaceuticals detected in biosolids in New Zealand studies.

Class	Pharmaceutical compound	Concentration (µg/kg)[a]	Reference
Analgesics and NSAIDs	Acetaminophen	76	CIBR (2013)
		<5[b]	Gielen (2007)
		<5[c]	Gielen (2007)
		detected	CIBR (2014)
	Codeine	ND	CIBR (2013)
	Diclofenac	8	CIBR (2013)
		detected	CIBR (2014)
	Ibuprofen	ND	CIBR (2013)
		299±4[b]	Gielen (2007)
		41±41[c]	Gielen (2007)
	Indomethacin	ND	CIBR (2013)
	ketoprofen	ND	CIBR (2013)
	Mefenamic acid	6	CIBR (2013)
	Naproxen	47	CIBR (2013)
		<5[b]	Gielen (2007)
		<5[c]	Gielen (2007)
		26.9	Wang et al. (2018)
	Phenazone	ND	CIBR (2013)
	Phenylbutazone	ND	CIBR (2013)
	Propyphenazone	ND	CIBR (2013)
Antibiotics	Azithromycin	BLD	CIBR (2013)
	Chloramphenicol	ND	CIBR (2013)
	Ciprofloxacin	219	CIBR (2013)
	Clarithromycin	4	CIBR (2013)
	Danofloxacin	ND	CIBR (2013)

Table B.1 continued. Concentrations of pharmaceuticals detected in biosolids in New Zealand studies.

Class	Pharmaceutical compound	Concentration (µg/kg)[a]	Reference
Antibiotics	Erythromycin	BLD	CIBR (2013)
		11.5	Wang et al. (2018)
	Flumequine	ND	CIBR (2013)
	Josamycin	BLD	CIBR (2013)
	Metronidazole	ND	CIBR (2013)
	Nifuroxazide	36	CIBR (2013)
	Norfloxacin	BLD	CIBR (2013)
	Roxithromycin	BLD	CIBR (2013)
	Sulfadiazine	9	CIBR (2013)
	Sulfamethazine	3	CIBR (2013)
	Sulfamethoxazole	15	CIBR (2013)
	Trimethoprim	5	CIBR (2013)
	Tylosin	BLD	CIBR (2013)
Anti-asthmatic	Clenbuterol	ND	CIBR (2013)
	Salbutamol	ND	CIBR (2013)
Anti-diabetic	Glibenclamide	BLD	CIBR (2013)
Antihistamine/anti-ulcer	Cimetidine	10	CIBR (2013)
	Famotidine	2	CIBR (2013)
	Ranitidine	23	CIBR (2013)
Anti-hypertensives	Enalapril	ND	CIBR (2013)
	Lisinopril	ND	CIBR (2013)
Blood lipid regulators/statins	Atorvastatin	17	CIBR (2013)
	Bezafibrate	8	CIBR (2013)
	Clofibric acid	ND	CIBR (2013)
	Fenofibrate	67	CIBR (2013)
	Gemfibrozil	1	CIBR (2013)
		13.6	Wang et al. (2018)
	Mevastatin	ND	CIBR (2013)
	Pravastatin	ND	CIBR (2013)
Beta blockers	Atenolol	ND	CIBR (2013)
	Betaxolol	ND	CIBR (2013)
	Carazolol	ND	CIBR (2013)
	Metoprolol	42	CIBR (2013)
		detected	(CIBR 2014)
	Nadolol	1	CIBR (2013)
	Pindolol	ND	CIBR (2013)
	Propranolol	114	CIBR (2013)
	Sotalol	7	CIBR (2013)
	Timolol	ND	CIBR (2013)
Anti-convulsant	Carbamazepine	105	CIBR (2013)
		<5[b]	Gielen (2007)
		49±4[c]	Gielen (2007)
		52.8	Wang et al. (2018)
		26.6	Wang et al. (2018)

Table B.1 continued. Concentrations of pharmaceuticals detected in biosolids in New Zealand studies.

Class	Pharmaceutical compound	Concentration (µg/kg)*	Reference
Diuretic	Furosemide	8	CIBR (2013)
	Hydrochlorothiazide	4	CIBR (2013)
Psychiatric	Amitriptyline	<5[b]	Gielen (2007)
		<5[c]	Gielen (2007)
	Butabital	ND	CIBR (2013)
	Diazepam	ND	CIBR (2013)
	Diltiazem	<248[b]	Gielen (2007)
	Fluoxetine	ND	CIBR (2013)
	Lorazepam	ND	CIBR (2013)
	Paroxetine	ND	CIBR (2013)
	Pentobarbital	10	CIBR (2013)
	Phenobarbital	ND	CIBR (2013)
	Thioridazine	<259[b]	Gielen (2007)
		<259[c]	Gielen (2007)
Steroid hormone	17a-ethinyl estradiol	185±185	Gielen (2007)
		<5[c]	Gielen (2007)

BLD – below detection limit; ND – not detected.
[a] Mean ± standard error, where indicated.
[b] primary solids
[c] final solids.

Table B.2: Concentrations of pharmaceuticals and several personal care products detected in environmental waters in New Zealand studies.

Therapeutic group	Pharmaceutical compound	Concentration (ng/l)			Reference
		Mean	Min	Maximum	
Analgesics/NSAIDs	Acetaminophen	ND			Bernot et al. (2019)
	Codeine	ND			Bernot et al. (2019)
	Ibuprofen	ND			Bernot et al. (2019)
	Naproxen	ND			Bernot et al. (2019)
	Norcodeine[a]	ND			Bernot et al. (2019)
Antibacterial	Triclocarban	ND			Bernot et al. (2019)
	Triclosan	ND			Bernot et al. (2019)
Antibiotic	Azithromycin	ND			Bernot et al. (2019)
	Chloramphenicol	ND			Bernot et al. (2019)
	Erythromycin	ND			Bernot et al. (2019)
	Sulfamerazine	ND			Bernot et al. (2019)
	Sulfamethoxazole	ND			Bernot et al. (2019)
	Sulfathiazole	ND			Bernot et al. (2019)
	Trimethoprim	ND			Bernot et al. (2019)
Anti-asthmatic	Salbutamol	ND			Bernot et al. (2019)
Anti-convulsant	Carbamazepine		9.7	26	Bernot et al. (2019)
Antihistamine	Cimetidine	ND			Bernot et al. (2019)
	Diphenhydramine	ND			Bernot et al. (2019)
	Ranitidine	ND			Bernot et al. (2019)
Artificial sweetener	Sucralose	ND			Bernot et al. (2019)
Blood lipid regulators	Gemfibrozil	ND			Bernot et al. (2019)
Insect repellent	DEET		5.5	510	Bernot et al. (2019)
Psychiatric drugs	Desvenlafaxine	ND			Bernot et al. (2019)
	Fluoxetine	ND			Bernot et al. (2019)
	Venlafaxine	ND			Bernot et al. (2019)
Stimulant	Caffeine		74	77	Bernot et al. (2019)
	Cotinine[b]		7.4	24	Bernot et al. (2019)
	Paraxanthine[c]	ND			Bernot et al. (2019)
Veterinary Antibiotic	Carbadox	ND			Bernot et al. (2019)
	Lincomycin	ND			Bernot et al. (2019)
	Sulfadimethoxine	ND			Bernot et al. (2019)
	Tylosin	ND			Bernot et al. (2019)

ND – not detected

[a] metabolite of codeine

[b] metabolite of nicotine

[c] metabolite of caffeine

Table B.3: Concentrations of pharmaceuticals and several personal care products detected in aquatic sediments in New Zealand studies.

Class	Pharmaceutical compound	Concentration (ng/g)		Reference
		Mean[a]	Maximum	
Analgesic/NSAID	Acetaminophen	ND		Bernot et al. (2019)
		7.66±1.05	10.79	Stewart (2013)
	Codeine	ND		Bernot et al. (2019)
	Diclofenac	1.95±0.57		Stewart (2013)
	Ibuprofen	ND		Bernot et al. (2019)
	Naproxen	ND		Bernot et al. (2019)
		5.5[b]	5.5	Stewart (2013)
	Norcodeine	ND		Bernot et al. (2019)
Antibiotic	Azithromycin	ND		Bernot et al. (2019)
	Clarithromycin	1.45±0.39		Stewart (2013)
	Chloramphenicol	ND		Bernot et al. (2019)
	Erythromycin	ND		Bernot et al. (2019)
	Roxythromycin	1.28±0.46		Stewart (2013)
	Sulfamerazine	ND		Bernot et al. (2019)
	Sulfamethazine	0.44[b]		Stewart (2013)
	Sulfamethoxazole	ND		Bernot et al. (2019)
	Sulfathiazole	ND		Bernot et al. (2019)
	Trimethoprim	ND		Bernot et al. (2019)
		0.23±0.08		Stewart (2013)
Antibacterial	Triclocarban	ND		Bernot et al. (2019)
	Triclosan	ND		Bernot et al. (2019)
Anti-asthmatic	Clenbuterol	0.75±0.44		Stewart (2013)
	Salbutamol	ND		Bernot et al. (2019)
		0.53[b]		Stewart (2013)
Anti-convulsant	Carbamazepine	ND		Bernot et al. (2019)
		0.67±0.15		Stewart (2013)
Anti-histamine/anti-ulcer	Cimetidine	ND		Bernot et al. (2019)
		0.94±0.37		Stewart (2013)
	Diphenhydramine	ND		Bernot et al. (2019)
	Famotidine	0.70[b]		Stewart (2013)
	Ranitidine	ND		Bernot et al. (2019)
		1.16±0.15		Stewart (2013)
Beta blockers	Metoprolol	2.06±0.30		Stewart (2013)
	Nadolol	0.31±0.15		Stewart (2013)
	Pindolol	0.41±0.18		Stewart (2013)
	Sotalol	0.92±0.17		Stewart (2013)
	Timolol	0.80[b]		Stewart (2013)
Blood lipid regulator and statins	Bezafibrate	0.16±0.02		Stewart (2013)
	Fenofibrate	1.38±0.20		Stewart (2013)
	Gemfibrozil	ND		Bernot et al. (2019)
Diuretic	Hydrochlorothiazide	0.38±0.02		Stewart (2013)
Insect repellent	DEET	7.9	58	Bernot et al. (2019)
Psychiatric drugs	Desvenlafaxine	ND		Bernot et al. (2019)
	Fluoxetine	ND		Bernot et al. (2019)
	Venlafaxine	ND		Bernot et al. (2019)

Table B.3 continued. Concentrations of pharmaceuticals and several personal care products detected in aquatic sediments in New Zealand studies.

Class	Pharmaceutical compound	Concentration (ng/g)		Reference
		Mean[a]	Maximum	
Steroid hormones	17a-ethinyl estradiol (EE2)	ND		Stewart et al. (2014)
Stimulant	Caffeine	ND		Bernot et al. (2019)
	Cotinine	ND		Bernot et al. (2019)
	Paraxanthine	ND		Bernot et al. (2019)
Veterinary antibiotic	Carbadox	ND		Bernot et al. (2019)
	Lincomycin	ND		Bernot et al. (2019)
	Sulfadimethoxine	ND		Bernot et al. (2019)
	Tylosin	ND		Bernot et al. (2019)

ND – not detected

[a] Mean ± SE

[b] Single sample rather than mean value; was only measured at one site.

Table B.4: Concentrations of pharmaceuticals detected in groundwater in New Zealand studies.

Class	Pharmaceutical compound	%	Concentration (ng/L)		Reference
			Mean	Max	
Analgesic/NSAIDs	Acetaminophen	6	32.5	96.8	Close and Humphries (2019)
		25	5.59	6.19	Humphries et al. (2024)
	Diclofenac	4	10.5	14	Moreau et al. (2019)
		6	37.1	98	Close and Humphries (2019)
	Hydrocodone	2	20	20	Moreau et al. (2019)
	Ibuprofen	7	44.7	175	Close and Humphries (2019)
		0			Moreau et al. (2019)
	Lidocaine	9	45	140	Moreau et al. (2019)
	Mefenamic acid	5	88	120	Moreau et al. (2019)
	Methadone	2	6.5	6.5	Moreau et al. (2019)
	Naproxen	4	25.4	57.3	Close and Humphries (2019)
	Oxycodone	2	13	13	Moreau et al. (2019)
	Tramadol	7	299	620	Moreau et al. (2019)
Antibiotics	Oxolinic acid	2	2.3	2.3	Moreau et al. (2019)
	Sulfamethoxazole	13	83	260	Moreau et al. (2019)
		75	0.91	1.67	Humphries et al. (2014)
Antibacterials	Sulfanilamide	11	15.3	25	Moreau et al. (2019)
Antineoplastics	Cyclophosphamide	2	6.4	6.4	Moreau et al. (2019)
Anti-arrhythmics	Flecainide	2	6	6	Moreau et al. (2019)
Anti-convulsants	Carbamazepine	9	203	620	Moreau et al. (2019)
		5	35.1	973	Close and Humphries (2019)
	10,11-Dihydroxycarbazepine[b]	4	1,055	1,200	Moreau et al. (2019)
	Lamotrigine	7	273	770	Moreau et al. (2019)
	Oxcarbazepine	2	18	18	Moreau et al. (2019)
	Phenobarbital	5	48	66	Moreau et al. (2019)
Anti-histamines	Cetirizine	2	660	660	Moreau et al. (2019)
Anti-hypertensives	Clonidine	2	detected[a]		Moreau et al. (2019)
	Irbesartan	5	31	68	Moreau et al. (2019)
Beta blockers	Atenolol	2	2	2	Moreau et al. (2019)
	Celiprolol	4	100	140	Moreau et al. (2019)
	Metoprolol	4	detected[a]		Moreau et al. (2019)
	Sotalol	5	243	650	Moreau et al. (2019)
Diuretics	Furosemide	2	34	34	Moreau et al. (2019)
	Hydrochlorothiazide	9	240	800	Moreau et al. (2019)
Blood lipid regulators and statins	Simvastatin	2	30	30	Moreau et al. (2019)
Psychiatric	Clozapine	2	42	42	Moreau et al. (2019)
	Oxazepam	2	11	11	Moreau et al. (2019)
	Venlafaxine	4	1.4	2.0	Moreau et al. (2019)

Table B.4 continued: Concentrations of pharmaceuticals detected in groundwater in New Zealand studies.

Class	Pharmaceutical compound	%	Concentration (ng/L)		Reference
			Mean	Max	
Steroid hormones	Estrone (E1)	5	1.8	6.2	Close and Humphries (2019)
	17α-estradiol (17αE2)	3	2.5	5.2	Close and Humphries (2019)
	17β-estradiol (17βE2)	0	ND		Close and Humphries (2019)
	Estriol (E3)	2	2.1	3.1	Close and Humphries (2019)
	17α-ethinyl estradiol (EE2)	<1	1.5	1.5	Close and Humphries (2019)
	Mestranol	2	4.4	6.8	Close and Humphries (2019)

ND – not detected.

[a] detected but not quantified

[b] carbemazapine metabolite

APPENDIX C: WASTEWATER TREATMENT PROCESSES

The following is a summary of different levels and types of wastewater treatment processes, included for ease of reference in supporting the discussion of pharmaceutical removal during wastewater treatment in Chapter 4. The information provided in this section has been summarised primarily from von Sperling (2007), Peake et al (2016), WaterNZ (2017) and Beca et al. (2020), where the reader can find further information. Parallel processes that form an essential part of an effective wastewater treatment train but are not directly responsible for the treatment of liquid wastewater effluent (eg, digestion of sludges or dewatering of solids) have not been included.

Preliminary treatment

Preliminary treatment is a physical processes whereby influent wastewater arriving at the WWTP is passed through series of screens to remove gross solids, rubbish, debris and large particles later than 2-5 cm in diameter. A series of smaller mesh screens are used to remove smaller solids, before wastewater often passes to a settling tank or 'grit chamber' to remove smaller particles such as grits and sands that may cause damage to equipment in the plant or compromise treatment efficiency. This is especially important where a network contains stormwater connections (ie, combined storm and sanitary sewers) or experiences significant inflow, as these flows contain large amounts of grit and debris. Solid materials that have been separated are removed and typically landfilled.

Primary treatment

Primary treatment is used for the removal of settleable suspended solids that remain after preliminary treatment. Screened effluents pass slowly through a settling tank or basin with a retention time of several hours; solids are removed by sedimentation, while materials that float (eg greases and oils) are removed by skimming. Primary treatment may remove 40-70% of the suspended solids, producing a primary sludge at the bottom of the tank or pond that requires stabilisation[25]. Primary treatment does not remove colloidal or dissolved constituents/contaminants. Some removal of BOD (often 25-40%) can be achieved by primary treatment. Treated primary effluent usually undergoes further treatment within the WWTP, while sludge may be removed and treated, or incinerated or landfilled. The efficiency of primary treatment in removing suspended solids and associated BOD may be enhanced through the addition of coagulants such as aluminium sulfate or ferric chloride, known as 'advanced primary treatment' or 'chemically-enhanced primary treatment.'

[25] Stabilisation is the conversion of organic matter in wastewater to carbon dioxide and water by microorganisms during respiration (the oxidation of organic materials to provide energy to support growth and reproduction). Carbon dioxide and water do not cause water quality issues or pollution, and are therefore considered 'stable' components, hence the term, stabilisation.

Types of primary treatment include primary sedimentation or settling tanks, primary clarifiers, and primary lagoons. The simplest forms of primary treatment are primary lagoons that facilitate both the settling of solids and the stabilisation of sludge within the lagoon.

Secondary treatment

Secondary treatment is used for further removal of remaining suspended solids and some non-settleable solids, and biodegradable organic matter, largely though biological processes (and therefore sometimes called secondary biological treatment). Microorganisms (largely bacteria, but also protozoa) present in secondary treatments consume organic matter present in the wastewater and convert it to biomass as they grow and reproduce; these processes are largely aerobic, however, some systems may be configured to support anaerobic bacteria. Secondary treatment processes may be classified as fixed-film (or attached-growth) systems or suspended-growth systems, based on the format of the microbial biomass. Most systems include a clarification step (ie, a secondary clarifier) to settle out and separate any biological floc, which may be returned to and reused within the biological system, or disposed of. Waste stabilisation ponds also commonly provide secondary biological treatment. Secondary treatment effluents are produced that are relatively free of suspended materials, and are either discharged to the environment or further treated within the WWTP. Microorganisms within secondary systems can be sensitive to changes in pH, variable loading of organic matter or the presence of toxic contaminants. Disinfection may be included in some secondary treatment systems after biological treatment and clarification has occurred, as it requires low concentrations of organic matter and solids; it is not typical of waste stabilisation ponds.

Fixed systems. Fixed systems allow wastewater (usually as primary treated effluents) to come into contact with microorganisms embedded within a biofilm adhered to a fixed surface, in order to remove pollutants from wastewater.

Trickling filters. Especially used in older plants or those receiving variable loading. Primary treated effluent is spread onto and trickles through a surface/bed made of carbonised coal, limestone chips or specially-fabricated plastic media. Biofilms form on the media surface, and microorganisms (bacteria, protozoa or fungi) within these films consumed the organic material in the wastewater as it percolates through the filter.

Rotating biological contractor. Consists of a series of closely-spaced, parallel discs that are mounted on a rotating shaft suspended above a wastewater tank. Microorganisms grow on the surface of these discs, consuming and degrading organic constituents/contaminants within the wastewater as they pass through it.

Constructed wetlands. An artificial wetland that has been engineered to use the natural function of vegetation, soil and microorganisms to provide biological treatment of wastewater, greywater, stormwater or industrial effluents. Primary treatment is recommended where wastewaters contain a high amount of suspended solids and/or soluble organic matter.

Suspended growth systems. Suspended growth systems allow wastewater to come into contact with microorganisms that form flocs (aggregates) and are freely suspended or mixed in with the wastewater itself.

Conventional activated sludge (CAS). A common method of secondary treatment that itself covers a variety of mechanisms to promote the aerobic growth of bacterial floc that removes organic material during respiration and consumption of organic nutrients in influent wastewaters. Organic matter is either biologically oxidised to carbon dioxide or converted to additional biological floc (ie, biomass) by reproducing microorganisms. Nitrogenous materials (eg amino acids, ammonia) are converted to nitrogen gas via denitrification. Effluents from aerated CAS mixing chambers (also known as a reactor) pass to a clarifier, where suspended biological floc settles out; treated wastewater is discharged or sent for tertiary treatment, while settled floc is returned to the reactor for continued growth.

Sequencing batch reactor. A system that combines secondary treatment and settlement within one system, by intermittently turning the aerators on and off, so that biological AS reactions and subsequent settling occur in the same tank. Incoming wastewater is aerated to allow biological reaction, and after settling, the clarified effluent can be run off, before aeration returns the settled floc to the liquid mass without the need for separate sludge recirculation. The system requires precise control of timing, mixing and aeration, and is vulnerable to factors like intermittent power supply or improper maintenance.

Activated sludge with nutrient removal. Biological reactors can incorporate various anoxic, anaerobic and aerobic zones in specific, sequential configurations to allow the growth of specific microorganisms and redox conditions to facilitate nitrification, denitrification and phosphorous absorption, and hence the removal of nitrogen to the atmosphere and phosphorous to sludge, respectively. Examples of these system include Bardenpho processes.

Membrane bioreactors (MBRs). These are activated sludge systems using a membrane liquid-solid phase separation process. The membrane component, which is usually immersed in the aerated tank, uses low pressure microfiltration or ultrafiltration membranes to remove the need for a secondary clarifier, reducing their footprint and overcoming limitations associated with poor settling of sludge/floc that can be problematic CAS systems. This can allow for increased biomass, and therefore higher removal of both soluble and particularly biodegradable materials. MBRs are associated with increased capital and operational costs compared with conventional methods, and are less flexible or resilient during periods of peak flow.

Aerobic granulation. Aerobic granular sludge is formed by applying specific processes that favour the growth of certain microorganisms that form granules, a type of sludge that forms spherical compact structures with high settleability. The system allows for higher biomass, and improved settling avoids the requirement for secondary clarifiers. Aerobic granulation has been commercialised as the Nereda process.

Aerated lagoons and ponds. A low technology suspended-growth method of secondary treatment, using aerators floating on the surface to increase atmospheric oxygen transfer to the lagoon and mix lagoon contents. Basins may range in depth from 1.5 to 5m, and achieve high removal of BOD with retention of 1-10 days, but do not achieve the same level of mixing or performance as conventional activated sludge systems.

Emerging technologies. Includes Biological Aerated (or Anoxic) Filter (BAF), Integrated Fixed Film Activated Sludge, and Moving Bed Biological Reactors.

Waste stabilisation ponds. Waste Stabilisation Ponds (WSPs) are amongst the most common treatment system in New Zealand, with more than half of WWTPs being a pond-based system. For small communities, WSPs may comprise a single pond in which several treatment stages occur, while larger communities (eg 30,000 people) tend to have multiple-pond systems to optimise each treatment stage, often with enhancements to produce higher quality effluents. Waste stabilisation ponds are shallow earthen basins that are able to reduce the concentration of suspended solids, BOD, nitrogen, phosphorous and microbial pathogens, depending on their design. Typically, WSPs comprise a small but deep anaerobic section or separate pond (4-6 m deep) to reduce the high concentrations of BOD and suspended solids in influent wastewater. The high organic load combined with a lack of diffusive oxygen transfer and light penetration to support photosynthetic algae means anaerobic conditions predominate in this [section of the] pond, and the settled solids are decomposed by anaerobic bacteria. Wastewater then passes to a shallower (1.5-2 m deep) facultative section or pond, which is naturally aerated by diffusion of oxygen from the atmosphere and algal photosynthesis. The low velocity of wastewater through the pond(s) encourages continued settlement of suspended solids, so that the lower layers of the facultative pond (or section) are also anoxic and anaerobic zones where settled organic matter decomposes, while dissolved BOD and fine particulate matter remain suspended in the upper and middle layers of the pond where they are decomposed by aerobic and facultative bacteria. The retention time for wastewater within ponds can be in the order of several weeks, depending on the pond construction. Some ponds may have mechanical aeration or mild agitation in order to increase dissolved oxygen and increase the rate of decomposition, or to ensure adequate mixing and contact between biomass and organic matter, respectively. Finally, shallow maturation ponds (0.6-1.5 m deep) may be used to improve pathogen removal by optimising exposure to conditions such as UV radiation and temperature variation.

Tertiary treatment

Tertiary treatment, sometimes also called advanced treatment or effluent polishing, is designed to provide a final treatment stage to further stabilise and improve effluent quality before discharge to the environment. More than one tertiary treatment process may be used in order to target further removal of suspended solids (fine particulates or colloidal materials) or specific contaminant(s) (eg nutrients, toxic metals) that are not well-removed by previous treatment stages. Examples of tertiary wastewater treatment technologies include biological nutrient removal (BNR), membrane bioreactors (MBR, a combination of AS and membrane filtration but which can also be considered secondary treatment), coagulation-sedimentation, advanced membrane separation (eg, reverse osmosis), filtration/adsorption using sands or activated carbon, or advanced chemical oxidation processes. Tertiary treatment may also include disinfection to remove pathogens, occurring as a final step after other treatments; most commonly chlorination or ultraviolet (UV) treatment are used.

Quaternary treatment

Quaternary treatment, or 'fourth treatment stage,' is intended to remove a significant majority of micropollutants (eg, EOCs such as antibiotics, pesticides, industrial chemicals, nanoplastics) that are increasingly being recognised as being present at trace levels in urban wastewater and which have the potential to cause harm to receiving environments and/or public health, but which are not removed by conventional wastewater treatments (primary, secondary or tertiary). Many of these types of contaminants are not readily biodegradable and accumulate in the environment following discharge.

Quaternary treatment technologies may be similar to those used in tertiary treatment, including adsorption processes using activated carbon granules or powder, ozonation or ultrafiltration, or additional processes such as nanofiltration; often, combinations of these processes (eg activated carbon followed by ozonation) appear necessary to remove the majority of target contaminants.[26,27] New methods, such as utilizing enzymes produced by fungi, are being researched for their potential to assist in the degradation of certain compounds.

Quaternary treatment is currently utilised in some parts of Europe, including Germany, Sweden, Switzerland and the Netherlands. In 2024, changes to the European Commission's Urban Wastewater Treatment Directive (European Commission 2022) will require mandatory quaternary treatment consisting of micropollutant removal, notably via ozonation and/or filtering with activated carbon or advanced techniques like nanofiltration and membranes[28] by all WWTPs treating a wastewater load equivalent to >150,000 people as soon as practicable, extending to WWTPs treating an equivalent load of >10,000 people and discharging to sensitive areas by the end of 2045.[29,30]

[26] https://www.dutchwatersector.com/news/promising-fourth-stage-technologies-for-wastewater-treatment-revealed-at-aquatech-amsterdam
[27] https://www.geo.fu-berlin.de/en/v/iwrm/Implementation/technical_measures/Wastewater-treatment/Off-site-treatment/Sewage-Treatment-Plants/Fourth-treatment-stage/index.html
[28] https://www.europarl.europa.eu/RegData/etudes/BRIE/2023/739370/EPRS_BRI(2023)739370_EN.pdf
[29] https://www.europarl.europa.eu/news/en/press-room/20240408IPR20307/new-eu-rules-to-improve-urban-wastewater-treatment-and-reuse
[30] https://www.europarl.europa.eu/doceo/document/TA-9-2024-0222_EN.html#title1

APPENDIX D: REMOVAL RATES FOR PHARMACEUTICALS DURING WASTEWATER TREATMENT

Table D.1 is a intended a numeric complement to Figures 2 to 4 that illustrate the removal rates that have been reported in international literature for various pharmaceutical compounds. Data in the table has been compiled from a study of multiple WWTPs by Castiglioni et al. (2006) and reviews by Verlicchi et al. (2012), Luo et al. (2014), Peake et al. (2016) and Tran et al. (2018). The review by Peake et al. (2016) also includes details as to the treatment process that was used in each study.

Table D.1: Reported removal rates for pharmaceuticals during wastewater treatment.

Class	Pharmaceutical compound	% removal (reported range)	% removal (mean)*	Reference
Analgesics/ NSAIDs	Acetaminophen	<0 – 99		Tran et al. (2018)
		98.7 – 100		Luo et al. (2014)
			86 –100	Verlicchi et al. (2012)
			>98	Peake et al. (2016)
	Aspirin		81 – >99	Peake et al. (2016)
	Codeine	<0 – 98		Tran et al. (2018)
			82	Verlicchi et al. (2012)
	Diclofenac	<0 – 98		Tran et al. (2018)
		<0 – 81.4		Luo et al. (2014)
			3-63	Verlicchi et al. (2012)
	Ibuprofen		-22 – >99	Peake et al. (2016)
	Fenoprofen	98.6 – 100		Tran et al. (2018)
	Ibuprofen	<0 – 99.8		Tran et al. (2018)
		72 - 100		Luo et al. (2014)
		0 – 100	55	Castiglioni et al. (2006)
			-13 – 99	Verlicchi et al. (2012)
			-22 – >99	Peake et al. (2016)
	Indomethacin	7 – 98.6		Tran et al. (2018)
			<10-23	Verlicchi et al. (2012)
	Ketoprofen	51.5 – 91.9		Tran et al. (2018)
		10.8 – 100		Luo et al. (2014)
			30 – 92	Verlicchi et al. (2012)
	Mefenamic acid	<0 – 70.2		Luo et al. (2014)
			5 – 92	Verlicchi et al. (2012)
	Naproxen	<0 – 99.3		Tran et al. (2018)
		43.3 – 98.6		Luo et al. (2014)
			35 – 95	Verlicchi et al. (2012)
	Propyphenazone		38 – 42	Verlicchi et al. (2012)

Table D.1 continued. Reported removal rates for pharmaceuticals during wastewater treatment.

Class	Pharmaceutical compound	% removal (reported range)	% removal (mean)*	Reference
Analgesics/ NSAIDs	Salicylic acid	9 – 95.4		Tran et al. (2018)
		89.6 – 100		Luo et al. (2014)
	Tramadol		4	Verlicchi et al. (2012)
Antibiotics	Amoxicillin	69.9 – 99.7		Tran et al. (2018)
		49 – 100		Castiglioni et al. (2006)
			96	Verlicchi et al. (2012)
			49 – 100	Peake et al. (2016)
	Azithromycin	<0 – 99		Tran et al. (2018)
			39 – 74	Verlicchi et al. (2012)
	Cefaclor		98	Verlicchi et al. (2012)
	Cefalexin		53 – 100	Verlicchi et al. (2012)
	Cefotaxime		43 – 83	Verlicchi et al. (2012)
	Chloramphenicol	11.8 – 73.8		Tran et al. (2018)
	Chlortetracycline	31.4 – 97.8		Tran et al. (2018)
			85	Verlicchi et al. (2012)
	Ciprofloxacin	<0 – 100		Tran et al. (2018)
			18 – 96	Verlicchi et al. (2012)
		45 – 78	63	Castiglioni et al. (2006)
	Clarithromycin	0 – 24	0	Castiglioni et al. (2006)
		<0 – 99		Tran et al. (2018)
			5 – 83	Verlicchi et al. (2012)
	Clindamycin	<0 – 88.9		Tran et al. (2018)
	Doxycycline		14 – 100	Verlicchi et al. (2012)
	Enrofloxacin	0 – 67		Tran et al. (2018)
			38 – 70	Verlicchi et al. (2012)
	Erythromycin	26.6 – 77.7		Tran et al. (2018)
		<0 – 82.5		Luo et al. (2014)
		0	0	Castiglioni et al. (2006)
			3 – 35	Verlicchi et al. (2012)
			-22 – >99	Peake et al. (2016)
	Lincomycin	<0 – 100		Tran et al. (2018)
		0	0	Castiglioni et al. (2006)
			17 – 57	Verlicchi et al. (2012)
	Meropenem	80.7 – 92.6		Tran et al. (2018)
	Minocycline	44.8 – 86.9		Tran et al. (2018)
	Norfloxacin		-6 – 91	Verlicchi et al. (2012)
	Ofloxacin	<0 – 99		Tran et al. (2018)
		0 – 66	57	Castiglioni et al. (2006)
			13 – 84	Verlicchi et al. (2012)
	Oxytetracycline	54.6 – 96.3		Tran et al. (2018)
			4	Verlicchi et al. (2012)
	Penicillin V		60	Verlicchi et al. (2012)
	Roxithromycin		-80 – 46	Verlicchi et al. (2012)

Table D.1 continued. Reported removal rates for pharmaceuticals during wastewater treatment.

Class	Pharmaceutical compound	% removal (reported range)	% removal (mean)*	Reference
Antibiotics	Spiramycin	0 – 11	0	Castiglioni et al. (2006)
	Sulfadiazine		78 – 100	Verlicchi et al. (2012)
	Sulfadimethazine		100	Verlicchi et al. (2012)
	Sulfamethazine	<0 – 96.2		Tran et al. (2018)
			16 – 100	Verlicchi et al. (2012)
	Sulfamethoxazole	<0 – 99		Tran et al. (2018)
		4 – 88.9		Luo et al. (2014)
		0 – 84	24	Castiglioni et al. (2006)
			5 –100	Verlicchi et al. (2012)
			-138 – 100	Peake et al. (2016)
	Sulfapyridine		20 – 89	Verlicchi et al. (2012)
	Sulfathiazole		65 – 100	Verlicchi et al. (2012)
	Tetracycline	34 – 97		Tran et al. (2018)
			-88 – 72	Verlicchi et al. (2012)
	Trimethoprim	<0 – 97		Tran et al. (2018)
		<0 – 81.6		Luo et al. (2014)
			-56 – 85	Verlicchi et al. (2012)
			-40 – >99	Peake et al. (2016)
	Vancomycin	96.6 – 99.9		Tran et al. (2018)
Anti-asthmatic	Salbutamol	0 – 12	0	Castiglioni et al. (2006)
			95	Verlicchi et al. (2012)
Anti-convulsants	Carbamazepine	<0 – 83		Tran et al. (2018)
		<0 – 62.3		Luo et al. (2014)
		0	0	Castiglioni et al. (2006)
			-37 – 65	Verlicchi et al. (2012)
	Gabapentin	<0 – 95.6		Tran et al. (2018)
			99.5	Verlicchi et al. (2012)
	Phenobarbital		99.5	Verlicchi et al. (2012)
Anti-diabetics	Glenclibamide		45	Verlicchi et al. (2012)
Anti-histamine	Famotidine		60	Verlicchi et al. (2012)
	Loratadine		15	Verlicchi et al. (2012)
	Ranitidine	0 – 89	72	Castiglioni et al. (2006)
			25 – 42	Verlicchi et al. (2012)
Anti-hypertensives	Enalapril	4 – 100	69	Castiglioni et al. (2006)
Beta blockers	Bisoprolol		0	Verlicchi et al. (2012)
	Atenolol	<0 – 96		Tran et al. (2018)
		<0 – 81.6		Luo et al. (2014)
		0 – 76	21	Castiglioni et al. (2006)
			<10 – 76	Verlicchi et al. (2012)
			0 – 100	Peake et al. (2016)

Table D.1 continued. Reported removal rates for pharmaceuticals during wastewater treatment.

Class	Pharmaceutical compound	% removal (reported range)	% removal (mean)*	Reference
Beta blockers	Metoprolol	<0 – 58.7		Tran et al. (2018)
		<3 – 56.4		Luo et al. (2014)
			<10 – 31	Verlicchi et al. (2012)
			7 – 83	Peake et al. (2016)
	Propranolol	<0		Tran et al. (2018)
			0 – 59	Verlicchi et al. (2012)
	Sotalol		18 – 27	Verlicchi et al. (2012)
Blood lipid regulators and statins	Bezafibrate	48.4 – 95.8		Tran et al. (2018)
		9.1 – 70.5		Luo et al. (2014)
		0 – 98	30	Castiglioni et al. (2006)
			36 – >99	Verlicchi et al. (2012)
	Clofibric acid	27.7 – 71.8		Tran et al. (2018)
		<0 – 93.6		Luo et al. (2014)
		0 – 30		Castiglioni et al. (2006)
			28 – 84	Verlicchi et al. (2012)
	Gemfibrozil	0 – 100		Tran et al. (2018)
		<0 – 92.3		Luo et al. (2014)
			5 –68	Verlicchi et al. (2012)
	Pravastatin		59 – 62	Verlicchi et al. (2012)
Diuretics	Furosemide	0 – 62	15	Castiglioni et al. (2006)
	Hydrochlorothiazide	0 – 77	44	Castiglioni et al. (2006)
			<10 – 76	Verlicchi et al. (2012)
Psychiatric drugs	Diazepam		8	Verlicchi et al. (2012)
	Fluoxetine		33 – 55	Verlicchi et al. (2012)
			8 – 100	Peake et al. (2016)
	Norfluoxetine		48	Verlicchi et al. (2012)
	Paroxetine		91	Verlicchi et al. (2012)
	Sulpiride	<0 – 73.5		Tran et al. (2018)
	Valproic acid		>99	Verlicchi et al. (2012)
Steroid hormones	Estrone (E1)	0 – 100		Tran et al. (2018)
		74.8 – 90.6		Luo et al. (2014)
		0 – 29		Castiglioni et al. (2006)
			-35 –99	Verlicchi et al. (2012)
	Estradiol (E2)	92.6 - 100		Luo et al. (2014)
			22 – 98	Verlicchi et al. (2012)
	Estriol (E3)	18 – 100		Tran et al. (2018)
		100		Luo et al. (2014)
	17a-ethinyl estradiol	33 – 100		Tran et al. (2018)
		43.8 – 100		Luo et al. (2014)
			70 – 94	Verlicchi et al. (2012)
			-14 – 90	Peake et al. (2016)

Table D.1 continued. Reported removal rates for pharmaceuticals during wastewater treatment.

Class	Pharmaceutical compound	% removal (reported range)	% removal (mean)*	Reference
X-ray contrasts	Iohexol	7.3 – 90		Tran et al. (2018)
	Iopamidol	<0 – 53.4		Tran et al. (2018)
	Iopromide	31 – 90		Tran et al. (2018)
			-32 – 50	Verlicchi et al. (2012)
Other	Clotrimazole		31	Verlicchi et al. (2012)
	Triclosan		69	Verlicchi et al. (2012)

*note that Verlicchi et al. (2012) and Peake et al. (2016) report the range of mean values for studies reviewed (for compounds where multiple studies were included; otherwise the mean for a single study is stated). Castiglioni et al. (2006) report the median value for removal across all plants and all seasons during their study, as well as the overall range in removal for individual sampling events.

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