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He Pūtaiao, He Tāngata

Assessment of the potential health hazard posed by environmental exposure to cytotoxic pharmaceuticals in New Zealand

May 2023

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PREPARED FOR: **Ministry of Health**

CLIENT REPORT No: **FW23004**

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ACKNOWLEDGEMENTS

The authors would like to thank Te Whatu Ora Data Services for provision of dispensing data.

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Although they are designed to treat human illnesses and disease, exposure to pharmaceuticals present in the environment may pose a hazard to human health, particularly in sensitive subpopulations such as children and pregnant women. The potential for pharmaceuticals to enhance the evolution of antimicrobial resistance should also not be discounted.

The aim of this report was to conduct a hazard assessment for pharmaceuticals present in wastewater, specifically focused on one of the most hazardous groups of pharmaceuticals – cytotoxic drugs. To assess if these drugs are potentially present in wastewater in New Zealand, information on dispensing amounts, excretion in urine and/or faeces, ways in which the drug may reach wastewater, the effect of wastewater treatment, and detections in wastewater internationally was assembled. Where these drugs are present in wastewater, people may be exposed due to accidental exposure to untreated wastewater or to surface waters to which wastewater effluents are discharged, particularly where these drugs are not completely removed by treatment processes.

Pharmaceuticals can enter the wastewater network via excretion in urine and/or faeces. They can also enter in effluents from the pharmaceutical industry, veterinary hospitals and incorrect disposal of unused medicines (eg, pouring down the sink or flushing down the toilet). However, there are strict rules around how these drugs should be disposed of, which will be discussed briefly in this report.

In New Zealand, cytotoxic drugs are mostly used in cancer treatment, but some are also used to treat other health conditions including idiopathic pulmonary fibrosis, rheumatoid arthritis and psoriasis. Based on information on drugs dispensed by community pharmacies, obtained from Te Whatu Ora, more than 60 different cytotoxic drugs were found to be dispensed in New Zealand in 2021 and 2022. For 21 of these drugs 5 kg or more was dispensed annually (based on mass not potency and estimated based on summation of different formulations). These drugs include antimetabolites (capecitabine, fluorouracil, mercaptopurine, methotrexate, gemcitabine, cytarabine), alkylating agents (dacarbazine, cyclophosphamide, ifosfamide), protein kinase inhibitors (imatinib, alectinib, nilotinib, palbociclib, nintedanib, pazopanib, dasatinib), monoclonal antibodies and antibody drug conjugates (pertuzumab), cytotoxic antibiotics and related substances (bleomycin) and other antineoplastic agents (hydroxycarbamide, venetoclax, olaparib). While these 21 most highly dispensed drugs were selected as targets for further hazard assessment, there were another 8 drugs dispensed more than 5,000 times, and another 15 drugs dispensed at least 1,000 times during 2022. While the overall quantity of these drugs was lower, many are cytotoxic at very low concentrations. These additional drugs are not reviewed in this report but may warrant future consideration.

The first step in this hazard assessment involved determining whether the target drugs had previously been detected in wastewater. For 10 of these drugs (capecitabine, dacarbazine, imatinib, fluorouracil, methotrexate, cyclophosphamide, gemcitabine, cytarabine, bleomycin and ifosfamide) studies confirming their presence in municipal wastewater were identified. For six of these (capecitabine, fluorouracil, methotrexate, cyclophosphamide, gemcitabine and ifosfamide), studies have also confirmed their presence in hospital wastewater.

The next step in this assessment was to determine what is known about excretion of these drugs in urine and/or faeces, their biodegradability and removal from wastewater. Twenty of the target drugs were found to be excreted in urine and/or faeces, to varying extents. Information on biodegradability could only be identified for eight of these drugs, although these studies were often conflicting. Limited information on removal from wastewater was identified.

Overall, for the 10 drugs previously detected in wastewater, it is possible that they may also be present in wastewater in New Zealand and therefore pose a health hazard. However, this would need to be confirmed by collection and testing of local samples. For the remaining 11 drugs, there was insufficient information to determine whether these drugs may be present in wastewater. As such, studies assessing their presence in wastewater are also needed.

Where these target drugs are present in wastewater this may lead to contamination of other aquatic matrices including surface and ground waters. Assessment of published literature found that eight of these drugs (capecitabine, imatinib, methotrexate, cyclophosphamide, gemcitabine, cytarabine, bleomycin, ifosfamide) have been found in surface waters. In addition, methotrexate and cyclophosphamide have been detected in ground water and cyclophosphamide and bleomycin detected in drinking water. If any of the 21 target drugs are identified in wastewater in New Zealand, studies assessing their presence in surface waters, groundwater and/or drinking water may be warranted.

2. INTRODUCTION

Pharmaceuticals are natural or synthetic chemicals which contain active ingredients designed to treat human, or animal, illnesses and diseases. However, where these chemicals are released to the environment, they may pose a human health hazard due to exposure to higher than recommended daily doses, chronic (long-term) exposure, exposure of vulnerable subpopulations (eg, pregnant women, children, those with drug allergies), or exposure to pharmaceutical mixtures (Rowney et al 2009, WHO 2012). Pharmaceuticals present in the environment may also contribute to the development and spread of antimicrobial resistance[1].

Pharmaceuticals have been identified in a range of aquatic environments, including wastewater, surface waters, ground water and drinking water (WHO 2012). The aim of this report is to determine whether the presence of these chemicals in wastewater and other aquatic environments in New Zealand is likely to pose a human health hazard. Given the wide variety of pharmaceuticals available, this first stage assessment will focus on one of the most hazardous classes of pharmaceuticals – cytotoxic drugs.

Cytotoxic drugs are most well-known for their role in cancer therapy. According to the 2020 World Health Organization report on cancer there were 18.1 million new cancer cases globally in 2018, and this is predicted to rise to 29.4 million by 2040 (WHO 2020). This is due, at least in part, to increasing average population age and improvements in detection techniques[2]. In New Zealand, cancer cases rose from 21,050 in 2011[3] to 27,024 in 2020, although the age standardised rates remained similar (335.9 and 337.4 cases per 100,000 people in 2011 and 2020 respectively)[4]. This increase in total cases will inevitably lead to increased usage of cytotoxic drugs, potentially resulting in their increased presence in the environment.

2.1 WHAT ARE CYTOTOXIC DRUGS?

Cytotoxic drugs, also known as antineoplastic agents (Negreira et al 2014b), are a class of pharmaceuticals designed to interrupt cell replication, inhibit DNA synthesis and damage cellular DNA (Kovalova et al 2009). These drugs predominantly act on rapidly dividing cells such as T lymphocytes, and as such are both immunosuppressive and anti-inflammatory (Brogan & Dillon 2000). Although initially designed for cancer treatment, the immunosuppressive 'side-effect' of these drugs has been exploited to treat non-malignant diseases with autoimmune mechanisms, such as rheumatoid arthritis and inflammatory bowel disease (Brogan & Dillon 2000).

[1] https://www.unep.org/explore-topics/chemicals-waste/what-we-do/emerging-issues/antimicrobial-resistance-global-threat Accessed 9 May 2023
[2] https://bpac.org.nz/bpj/2015/october/chemotherapy.aspx Accessed 15 February 2023
[3] https://www.health.govt.nz/publication/cancer-new-registrations-and-deaths-2011 Accessed 4 April 2023
[4] https://www.tewhatuora.govt.nz/our-health-system/data-and-statistics/new-cancer-registrations-2020/ Accessed 4 April 2023

Cytotoxic drugs are classified into several groups by the Anatomical Therapeutic Chemical (ATC) classification system[5]:

- L01A Alkylating agents
- L01B Antimetabolites
- L01C Plant alkaloids and other natural products
- L01D Cytotoxic antibiotics and related substances
- L01E Protein kinase inhibitors
- L01F Monoclonal antibodies and antibody drug conjugates
- L01X Other antineoplastic agents

2.2 SOURCES OF CYTOTOXIC DRUGS TO THE ENVIRONMENT

There are several potential routes for cytotoxic drugs to enter the environment, as summarised in Figure 1. Although not all pharmaceuticals may be persistent in the environment, some of these contaminants may be considered pseudo-persistent due to their constant release into aquatic environments (Ebele et al 2017).

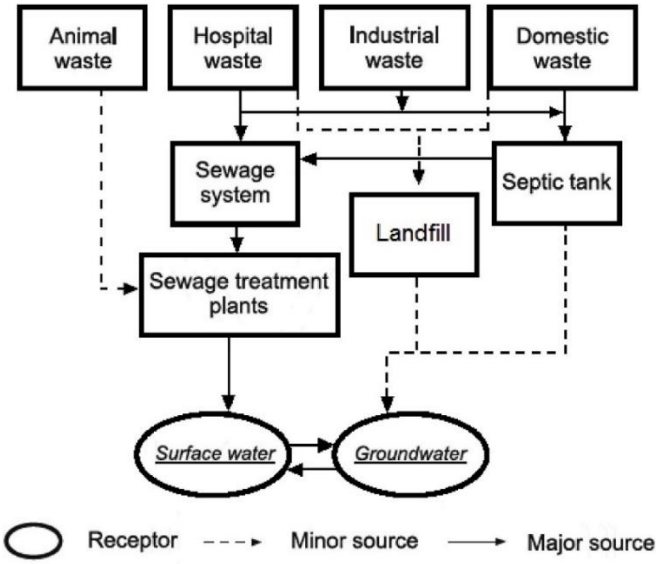

Figure 1 Potential sources of cytotoxic pharmaceuticals to water

Reproduced from Jureczko and Kalka (2020).

Wastewater represents a major source for cytotoxic drugs into aquatic environments, as not all cytotoxic drugs are completely removed by conventional wastewater treatment processes, resulting in these drugs being present in effluents discharged to surface waters (Nassour et al 2020).

[5] https://www.whocc.no/atc_ddd_index/?code=L01&showdescription=no Accessed 30 January 2023

The main source of cytotoxic drugs to wastewater is excretion by patients after medicinal use[6]. Following chemotherapy, the drug may be present in bodily excretions including urine, faeces and/or vomit, and be discharged to the wastewater network. It may also be present on contaminated surfaces or objects (eg, linens), and be discharged to the wastewater network during washing. Many human pharmaceuticals are known to not be completely metabolised by the body and are excreted either unchanged or slightly transformed, mostly as conjugates with polar molecules (Zounkova et al 2010). These polar conjugates are easily cleaved during wastewater treatment, which may result in transformation back to the original parent drug (Heberer 2002), potentially leading to negative removal efficiencies.

Cytotoxic drugs may also enter the municipal wastewater network in wastes from veterinary practices, as many of these chemicals are used in veterinary medicine[7]. Although faeces from animals being treated with cytotoxic drugs are to be discarded as cytotoxic waste by veterinary practices in New Zealand, these drugs may be discharged to the wastewater network during washing of contaminated bedding or enclosures[8]. Additionally, pet owners are advised to flush potentially contaminated faeces down the toilet[9].

In addition to these biological sources, cytotoxic drugs may also enter the municipal wastewater network in trade waste from the pharmaceuticals industry (Zhang et al 2013)[10]. In New Zealand, four companies are currently licensed to manufacture 'antineoplastic agents and immunosuppressive agents, other than steroid preparations'[11], however, no information as to the specific drugs or quantities being produced was readily publicly available. In addition, other pharmaceutical companies, universities and patient advocacy groups may utilise cytotoxic drugs in research and development activities[12].

Finally, cytotoxic drugs may also enter the municipal wastewater network through improper disposal of unused or expired medicines (eg, pouring medicines down the drain or toilet). Strict rules apply to disposal of cytotoxic drugs in New Zealand (see Section 2.4 below), and any unused or expired cytotoxic drugs should be returned to pharmacies for proper disposal. Improper disposal of these to landfill may also lead to contamination of aquatic environments due to leaching into ground and surface waters (Bound & Voulvoulis 2005).

[6] https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/pharmaceuticals-in-the-environment-pie/ Accessed 16 January 2023
[7] https://www.massey.ac.nz/massey/fms/Colleges/College%20of%20Sciences/IVABS/vetschool/IVMA%20/3_%20SOP%20CYtotoxic%20Drugs.pdf Accessed 31 January 2023
[8] https://www.massey.ac.nz/massey/fms/Colleges/College%20of%20Sciences/IVABS/vetschool/IVMA%20/3_%20SOP%20CYtotoxic%20Drugs.pdf Accessed 15 February 2023
[9] https://www.massey.ac.nz/massey/fms/Colleges/College%20of%20Sciences/IVABS/vetschool/IVMA%20/3_%20SOP%20CYtotoxic%20Drugs.pdf Accessed 15 February 2023
[10] https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/pharmaceuticals-in-the-environment-pie/ Accessed 16 January 2023
[11] https://www.medsafe.govt.nz/regulatory/licensed.asp Accessed 15 February 2023
[12] https://www.fmhs.auckland.ac.nz/en/sms/about/our-departments/auckland-cancer-society-research-centre/about-us/drug-development.html Accessed 20 February 2023

2.3 CYTOTOXIC DRUG USAGE IN NEW ZEALAND

In New Zealand, cytotoxic drugs are mainly used in the treatment of cancers[13]. However, some have also been approved for the treatment of non-cancer diseases including cyclophosphamide for treatment of rheumatoid arthritis[14], nintedanib for treatment of idiopathic pulmonary fibrosis[15], and methotrexate for treatment of rheumatoid arthritis and "severe, recalcitrant disabling psoriasis when other therapies [are] ineffective"[16].

A list of cytotoxic pharmaceuticals approved for usage in New Zealand was obtained from the New Zealand Formulary[17], and is appended in Table 11 together with dispensing data for 2017 – 2022 obtained from the Te Whatu Ora Pharmaceutical Collection on request. A summarised list of those drugs dispensed during 2021-2022 is presented in Table 1. It is important to note that data were only available for drugs dispensed from community pharmacies as it is based on claim and payment information from pharmacists for subsidised dispensings[18], and does not include all hospital-based dispensings.

Based on the community dispensing data provided by Te Whatu Ora, 21 drugs had an estimated 5 kg or more dispensed annually during 2021 and/or 2022 (based on mass not potency) (Table 1). However, caution must be taken when calculating total amounts dispensed as a given drug may be dispensed as different formulations and the base units of these may vary[19]. We have attempted to provide an overall estimation of the total amount of each drug dispensed, taking into consideration the variable base units. Information on the different formulations of these 21 drugs is provided in Table 12. Given the relatively large number of cytotoxic drugs dispensed in New Zealand, this report will focus on the 21 target drugs highlighted in bold italics in Table 1. The ATC classifications for these 21 drugs are listed in Table 2.

[13] https://www.nzf.org.nz/nzf_4381 Accessed 26 January 2023
[14] https://www.nzf.org.nz/nzf_4453 Accessed 26 January 2023
[15] https://www.nzf.org.nz/nzf_70790 Accessed 26 January 2023
[16] https://www.nzf.org.nz/nzf_4548 Accessed 26 January 2023
[17] https://www.nzf.org.nz/nzf_4381 Accessed 25 January 2023
[18] https://www.tewhatuora.govt.nz/our-health-system/data-and-statistics/pharmaceutical-data-web-tool/ Accessed 20 April 2023
[19] https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ Accessed 8 February 2023

Table 1 Cytotoxic drugs dispensed in New Zealand in 2021 and 2022

Drug	2022 dispensings			2021 dispensings		
	Total	Initial	Amount (kg)	Total	Initial	Amount (kg)
Hydroxycarbamide	32434	12734	***686.9***	31612	12201	***658.8***
Pertuzumab	2800	2800	***480.8***	2695	2695	***338.5***
Capecitabine	11584	9777	***371.4***	11867	10101	***389***
Dacarbazine	798	798	***81.6***	951	951	***90.4***
Fluorouracil sodium	76731	72461	***81.5***	72975	68766	***78.4***
Imatinib mesilate	3727	2254	***67.6***	3386	2128	***64.1***
Fluorouracil	20701	20701	***59.3***	22550	22550	***62.9***
Alectinib	665	304	***24.6***	631	281	***22.5***
Mercaptopurine	15599	6372	***24.6***	15541	6266	***24.2***
Venetoclax	1452	669	***23.4***	1281	641	***21.9***
Methotrexate	165706	111333	***22***	161045	107949	***22.9***
Nilotinib	891	373	***17.6***	837	361	***16.8***
Palbociclib	7265	3867	***17.3***	6806	3805	***16.6***
Cyclophosphamide	10952	9578	***15.6***	11439	10212	***16.7***
Nintedanib	1585	662	***14.1***	1255	522	***11.2***
Pazopanib	799	351	***13.5***	709	325	***11.9***
Gemcitabine HCl	5545	5545	***9.5***	5687	5687	***10***
Cytarabine	1699	1699	***8.8***	1844	1844	***9***
Olaparib	533	260	***8***	314	153	***4.4***
Bleomycin sulfate	828	828	***6.4***	976	976	***6.0***
Ifosfamide	1072	1072	***6.1***	1198	1198	***6.1***
Dasatinib	1656	693	4.9	1801	781	***5.4***
Carboplatin	8080	8080	4.1	7926	7926	4.2
Gefitinib	495	226	4.1	602	255	4.8
Trastuzumab	8181	8181	3.9	8654	8654	4.1
Erlotinib	897	403	3.5	950	453	3.8
Temozolomide	3127	2386	3.2	2728	1968	2.8
Vinorelbine	2362	2362	2.3	2308	2308	0.8
Pemetrexed	2178	2178	1.9	1861	1861	1.6

Drug	2022 dispensings			2021 dispensings		
	Total	Initial	Amount (kg)	Total	Initial	Amount (kg)
Carmustine	60	60	1.8	88	88	2.7
Irinotecan HCl	5579	5579	1.7	6159	6159	1.9
Paclitaxel	10577	10577	1.7	9844	9844	1.6
Ruxolitinib	2262	937	1.7	1870	770	1.4
Etoposide phosphate	3315	3315	1.3	3363	3363	1.4
Oxaliplatin	7476	7476	1.3	7939	7939	1.4
Tretinoin	35099	35083	1	29196	29171	0.9
Azacitidine	4998	4998	0.9	5701	5701	0.9
Pembrolizumab	4040	4040	0.9	4240	4240	0.9
Fludarabine phosphate	374	354	0.8	509	479	1.3
Sunitinib	998	635	0.8	991	630	0.8
Etoposide	1088	928	0.7	1010	887	0.7
Procarbazine HCl	477	407	0.6	448	378	0.6
Docetaxel	4031	4031	0.5	4179	4179	0.6
Doxorubicin HCl	5954	5954	0.5	6567	6567	0.5
Bendamustine HCl	2111	2111	0.4	3060	3060	0.5
Cisplatin	3322	3322	0.4	3447	3447	0.4
Daunorubicin	355	355	0.4	407	407	0.5
Durvalumab	168	168	0.3			
Trastuzumab emtansine	1050	1050	0.3	964	964	0.2
Epirubicin HCl	1300	1300	0.2	1393	1393	0.2
Melphalan	404	378	0.08	432	398	0.1
Arsenic trioxide	388	388	0.06	410	410	0.05
Bortezomib	9156	9156	0.04	9595	9595	0.04
Chlorambucil	550	434	0.04	634	477	0.05
Ibrutinib	<12	<12	0.04			
Lomustine	301	292	0.04	229	210	0.03
Nivolumab	138	138	0.04	53	53	0.02
Busulfan	374	233	0.02	404	216	0.02
Cetuximab	58	58	0.02	71	71	0.04

Drug	2022 dispensings			2021 dispensings		
	Total	**Initial**	**Amount (kg)**	**Total**	**Initial**	**Amount (kg)**
Cladribine	76	76	0.02	64	64	0.02
Everolimus	83	46	0.02	101	52	0.02
Vinblastine sulfate	1344	1344	0.01	1322	1322	0.01
Vincristine sulfate	4983	4983	0.01	5019	5019	0.01
Gemtuzumab ozogamicin	20	20	<0.02			
Dactinomycin	131	131	<0.01	149	149	<0.01
Idarubicin HCl	82	82	<0.01	139	139	<0.01
Mitomycin C	594	594	<0.01	598	598	0.01
Mitoxantrone	108	108	<0.01	85	85	<0.01

Data obtained from the Te Whatu Ora Pharmaceutical Collection on request. Drugs with more than 5 kg dispensed annually in 2021 and/or 2022 are indicated in bold italics. Initial dispensings refer to the number of times the drug was first dispensed to a named person on a given prescription, whereas total dispensings include both the initial dispensing and all repeat dispensings (eg, prescriptions are often dispensed with one initial dispensing and two repeat dispensings, which would be recorded as one initial dispensing and three total dispensings).

Table 2 ATC classifications for those cytotoxic drugs with an estimated 5 kg or more dispensed in New Zealand in 2021 and/or 2022

Drug	ATC classification		
Hydroxycarbamide	L01X	Other antineoplastic agents	https://www.whocc.no/atc_ddd_index/?code=L01XX05
Pertuzumab	L01F	Monoclonal antibodies and antibody drug conjugates	https://www.whocc.no/atc_ddd_index/?code=L01FD02
Capecitabine	L01B	Antimetabolite	https://www.whocc.no/atc_ddd_index/?code=L01BC06
Dacarbazine	L01A	Alkylating agents	https://www.whocc.no/atc_ddd_index/?code=L01AX04
Imatinib	L01E	Protein kinase inhibitors	https://www.whocc.no/atc_ddd_index/?code=L01EA01
Fluorouracil	L01B	Antimetabolite	https://www.whocc.no/atc_ddd_index/?code=L01BC02
Alectinib	L01E	Protein kinase inhibitors	https://www.whocc.no/atc_ddd_index/?code=L01ED03
Mercaptopurine	L01B	Antimetabolite	https://www.whocc.no/atc_ddd_index/?code=L01BB02
Venetoclax	L01X	Other antineoplastic agents	https://www.whocc.no/atc_ddd_index/?code=L01XX52
Methotrexate	L01B	Antimetabolite	https://www.whocc.no/atc_ddd_index/?code=L01BA01
Nilotinib	L01E	Protein kinase inhibitors	https://www.whocc.no/atc_ddd_index/?code=L01EA03
Palbociclib	L01E	Protein kinase inhibitors	https://www.whocc.no/atc_ddd_index/?code=L01EF01
Cyclophosphamide	L01A	Alkylating agents	https://www.whocc.no/atc_ddd_index/?code=L01AA01
Nintedanib	L01E	Protein kinase inhibitors	https://www.whocc.no/atc_ddd_index/?code=L01EX09
Pazopanib	L01E	Protein kinase inhibitors	https://www.whocc.no/atc_ddd_index/?code=L01EX03
Gemcitabine	L01B	Antimetabolite	https://www.whocc.no/atc_ddd_index/?code=L01BC05
Cytarabine	L01B	Antimetabolite	https://www.whocc.no/atc_ddd_index/?code=L01BC01
Olaparib	L01X	Other antineoplastic agents	https://www.whocc.no/atc_ddd_index/?code=L01XK01
Bleomycin	L01D	Cytotoxic antibiotics and related substances	https://www.whocc.no/atc_ddd_index/?code=L01DC01
Ifosfamide	L01A	Alkylating agents	https://www.whocc.no/atc_ddd_index/?code=L01AA06
Dasatinib	L01E	Protein kinase inhibitors	https://www.whocc.no/atc_ddd_index/?code=L01EA02

Data accessed 20 April 2023.

2.4 DISPOSAL OF CYTOTOXIC DRUGS IN NEW ZEALAND

Under the New Zealand Standard for the Management of Healthcare Waste (NZS 4304:2002) (Standards New Zealand 2002), cytotoxic waste[20] is considered a sub-category of hazardous waste and must be separated and disposed of by incineration or by discharge to the sewer, where the latter is approved by the local authority. However, the Resource Management (National Environmental Standards for Air Quality) Regulations 2004 prohibit the high-temperature incineration of hazardous waste in New Zealand[21]. Further a rapid review of territorial authority (ie, District and City Council) trade waste bylaws found that cytotoxic waste was consistently considered a prohibited characteristic, making it unacceptable for discharge to the wastewater system. As a result, all cytotoxic wastes must be exported for incineration overseas.

One exporter currently has a permit to export cytotoxic waste from New Zealand, as detailed in Table 3, although other companies may facilitate the collection and transport of wastes to an authorised exporter[22,23].

Table 3 Details of exporter permitted to export cytotoxic waste from New Zealand

Exporter	Waste product	Destination	Quantity (tonnes)	Expiry
International Waste Limited (Interwaste)	Cytotoxic contaminated waste	Australia	200	30/06/2023

Data from the New Zealand Environmental Protection Authority[24].

In New Zealand, patients with unwanted or expired medications, including cytotoxic drugs, are encouraged to dispose of them by returning them free of charge to community or hospital pharmacies for disposal[25] (Hanning et al 2022, Tong et al 2011b). However, a 2008 survey of 452 individuals found that the most popular methods to dispose of unwanted medications were to the wastewater network or household rubbish (Braund et al 2009). In particular, medications with a liquid formulation were more likely to be poured down the sink or the toilet, while solid (tablets, capsules) and semi-solid (ointments, creams) formulations tended to be discarded in the rubbish. Similar patterns are seen in international studies (Tong et al 2011a, Wheeler et al 2017), with the exception of Sweden, where a well-established and well-resourced national disposal scheme sees the majority of unwanted medications returned to the pharmacy for incineration (Persson et al 2009). Anecdotal evidence, including the discovery of medical and veterinary wastes in domestic recycling,

[20] Cytotoxic waste is defined as cytotoxic drugs, or material that is or may be contaminated with a cytotoxic drug.
[21] https://www.legislation.govt.nz/regulation/public/2004/0309/latest/DLM286835.html Accessed 14 February 2023
[22] https://www.nitrogenx.co.nz/cytotoxic/ Accessed 9 February 2023
[23] https://hitechdisposals.co.nz/waste-disposal/medical-waste-disposal/ Accessed 9 February 2023.
[24] https://www.epa.govt.nz/industry-areas/hazardous-substances/hazardous-waste/current-permit-holders/ Last updated 23 May 2023; Accessed 7 September 2023
[25] http://www.saferx.co.nz/brief-updates/dump-campaign/ Accessed 14 February 2023

further highlights the potential for improper disposal of at-home medical treatments in New Zealand[26, 27].In 2022, approximately 66% of cytotoxic drugs dispensed in New Zealand were solid formulations.

Table 4 Disposal practices for unused or unwanted medications from a selection of international studies

	Means of disposal*			Reference
	Sink or toilet	Household rubbish	Return to pharmacy	
New Zealand	56% liquid 20% solid <2% creams	24% liquid 51% solid 77% creams	18% liquid 25% solid 14% creams	Braund et al (2009)
US	35% sink 54% toilet		23%	Seehusen and Edwards (2006)
US	35%	54%	1%	Kuspis and Krenzelok (1996)
Australia	14%	55%		Wheeler et al (2017)
UK	12%	63%	22%	Bound and Voulvoulis (2005)
Malaysia	12%	63%	25%	Ariffin and Zakili (2019)
Sweden	0%	3%	43%	Persson et al (2009)

*Percentages may not add to 100% if respondents selected more than one disposal method or used methods other than those shown here (eg, burning, giving to other people).

Currently, there are few data available on the specific types of medications that are returned to pharmacies, including how many of these may be cytotoxic, or how these medications are subsequently disposed of by the pharmacy (Hanning et al 2022, Tong et al 2011b). A survey of 265 New Zealand pharmacies revealed that the most common methods for the disposal of solid and semi-solid formulations was through a third-party contractor (80% and 61% respectively), with liquids predominantly poured down the sink (45%) or toilet (7%) (Tong et al 2011b). In a study of the pharmaceutical wastes collected by a third-party contractor in Auckland, cytotoxic drugs were found to account for 0.7% of all audited waste, despite the requirement for them to be separated and destroyed by incineration, highlighting the potential for cytotoxic drugs to be improperly disposed of even where they have been returned to a pharmacy (Hanning et al 2022). Anecdotal evidence further suggests that some pharmacies may not be separating cytotoxic drugs from general pharmaceutical waste due to associated costs and health risks to staff, especially where they are not being funded

[26] https://www.stuff.co.nz/national/health/123411955/ratepayers-33k-cleanup-bill-after-blood-bags-medical-waste-thrown-in-with-recycling Accessed 14 February 2023
[27] https://www.stuff.co.nz/dominion-post/news/93705822/needles-sanitary-waste-and-pharmaceuticals-putting-waste-workers-at-risk Accessed 14 February 2023

by health authorities to receive and dispose of returned medications[28,29,30]. General pharmaceutical waste collected by third parties is treated by 'steaming' to ~140°C before being landfilled; however, there are concerns that while this material will be sterilised, the various pharmaceutically-active compounds may not be destroyed, and therefore have the potential to leach into the environment[31,32]. There is no information on whether cytotoxic drugs may be among those disposed of directly to the wastewater network (ie, down the sink or toilet) by pharmacy staff.

Overall, the contribution of pharmacies and public hospitals to the total load of pharmaceutical waste is low compared with manufacturing and research facilities; for example, Hanning et al (2022) estimated that approximately 9% of Auckland's pharmaceutical wastes originated from public hospitals and pharmacies. Further, cytotoxic waste is estimated to account for less than 1% of all healthcare waste in New Zealand (Bolton 2021). Thus, while the volumes of any cytotoxic drugs disposed of to wastewaters or landfill (and therefore, potentially leachates) are likely to be low, the available data does highlight the potential for disposal via this pathway. We were unable to obtain any information regarding the disposal of cytotoxic drugs from hospitals, veterinary clinics, pharmaceutical manufacturers or research facilities to understand the extent of compliance with the requirement to separate and export cytotoxic wastes for incineration (ie with NZS 4304:2002 and relevant trade waste bylaws).

[28] https://www.nzdoctor.co.nz/article/news/rangitikei-pharmacist-disputes-cytotoxic-waste-disposal-requirement Accessed 9 February 2023

[29] According to the articles in footnotes 27, 29 and 30, funding for pharmacies to dispose of returned medicines was previously administered by the relevant District Health Board (DHB). Some DHBs provided funding while others did not, and the service was reported as being inconsistent. There was no specific funding for the separate disposal of cytotoxic waste; this was considered to be part of the overall contract. The authors are unclear as to how such funding is administered following the establishment of Te Whatu Ora.

[30] https://www.rnz.co.nz/news/national/279943/medicine-disposal-'a-national-disaster' Accessed 4 April 2023

[31] https://www.rnz.co.nz/news/in-depth/380632/a-bitter-pill-why-can-t-we-recycle-medication Accessed 14 February 2023

[32] https://www.rnz.co.nz/news/national/279943/medicine-disposal-'a-national-disaster' Accessed 14 February 2023

3. CYTOTOXIC DRUGS IN WASTEWATER

Hospital wastewater is well-known to contain a variety of pharmaceutically active compounds (PhACs), including cytotoxic drugs, which, depending on the efficiency of the hospital wastewater treatment processes (if any) may be discharged to the municipal wastewater network in trade waste (Kumari et al 2020, Majumder et al 2021). Due to the increasing availability of oral formulations for many cytotoxic drugs, these drugs are now often able to be taken at-home rather than in hospital[33]. As such, residential wastewaters may also contain these drugs. Additionally, where these drugs are administered in a hospital setting, depending on the half-life if the particular drug, patients may return home whilst still excreting the cytotoxic agent (Zhang et al 2013). Indeed, a Spanish study noted that hospital effluents were not the main source of environmental contamination with some common chemotherapy drugs (eg, methotrexate, ifosfamide) (Negreira et al 2014a). Similarly, an assessment by Besse et al (2012) estimated that the majority of anticancer drugs entering French municipal wastewater treatment plants (WWTPs) were from residential rather than hospital effluents (Figure 2).

Several studies have identified cytotoxic drugs in municipal and hospital wastewaters. This section will provide an overview of some of these studies, many of which were identified using the German Environment Agency Pharmaceuticals in the Environment database[34]. Given the large number of cytotoxic drugs available, this report will focus on the 21 target drugs identified earlier in this report. Where available, information on excretion, biodegradability and removal of these drugs from wastewater will be discussed to assess the potential health hazard posed by the presence of these drugs in wastewater.

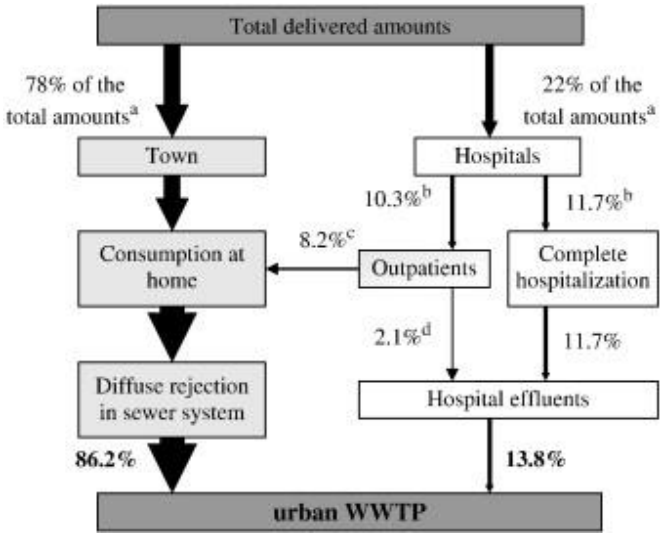

Figure 2 Theoretical input pathways for anticancer drugs to the aquatic environment

Reproduced from Besse et al (2012). Diffuse rejection refers to drugs being excreted to the wastewater network from various residential locations within the network, rather than all in the same location (ie, in hospital effluents).

[33] https://bpac.org.nz/bpj/2015/october/chemotherapy.aspx Accessed 15 February 2023
[34] https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0 Accessed 26 January 2023

3.1 PRESENCE IN MUNICIPAL WASTEWATER

Of the 21 drugs assessed in this report, international studies assessing their presence in wastewater were identified for ten: capecitabine, dacarbazine, imatinib, fluorouracil, methotrexate, cyclophosphamide, gemcitabine, cytarabine, bleomycin and ifosfamide (Table 5). All these drugs, except for bleomycin, have been detected in untreated municipal wastewater, with methotrexate and cyclophosphamide detected at the highest concentrations. All 10 of these drugs were detected in treated municipal wastewater, with methotrexate and ifosfamide detected at the highest concentrations.

3.2 PRESENCE IN HOSPITAL WASTEWATER

In contrast to the municipal wastewater studies discussed above, for many studies assessing the presence of the target drugs in hospital wastewater it was unclear whether these wastewaters had been treated, and if so, what treatment process was employed; as such, no distinction is made between treated or untreated hospital wastewaters in this report.

Of the 21 target drugs, studies assessing their presence in hospital wastewaters were identified for seven: capecitabine, fluorouracil, methotrexate, cyclophosphamide, gemcitabine, cytarabine and ifosfamide (Table 6). Of these seven drugs, only cytarabine was not detected in the assessed hospital wastewaters. Of the drugs detected, methotrexate, fluorouracil and ifosfamide were detected at the highest concentrations.

3.3 ASSESSMENT OF THE POTENTIAL HEALTH HAZARD DUE TO PRESENCE OF THE TARGET DRUGS IN WASTEWATER

To ascertain whether the 21 target drugs are likely to pose a significant health hazard when present in wastewater, this section will assess: a) whether these drugs are known to be excreted in urine and/or faeces, either unchanged or as a toxic metabolite; b) whether these drugs are likely to biodegrade; and c) what is known about the removal of these drugs from wastewater.

Data on excretion of these drugs in urine and/or faeces was predominantly sourced from drug monographs compiled in the British Columbia Cancer (BCC)[35] electronic cancer drug manual and are summarised in Table 7.

Several studies assessing the biodegradability of some these drugs have been identified, as summarised in Table 8. A range of standard biodegradability tests have been employed including activated sludge incubations, the Zahn-Wellens test (ZWT), closed bottle test, manometric respiration test, and degradation in a laboratory-scale sewage reactor. It is important to note that the concentrations used in these tests are often much higher than those found in wastewater, and results are sometimes conflicting (Booker et al 2014).

[35] http://www.bccancer.bc.ca/ Accessed 9 February 2023

Table 5 Summary of studies assessing presence of the 21 target cytotoxic drugs in municipal wastewater

Matrix	Pharmaceutical	Analyte	Countries not found in	Countries detected in	Max conc. (ng/L)
Untreated	Capecitabine	Parent		Canada, Greece, Slovenia, Spain, United Kingdom	158
	Dacarbazine	Parent		Greece	1124
	Imatinib	Parent		United Kingdom	368.3
	Fluorouracil	Parent	Brazil, Canada, France, Switzerland, USA	Slovenia, Spain	14
		FBAL		Brazil	13,500
	Methotrexate	Parent	Sweden, Tunisia, United Kingdom	Canada, China, Greece, Jordan, Slovenia, Spain	450,000
		Hydroxymethotrexate	Spain	Slovenia	366
	Cyclophosphamide	Parent	France, Norway, Sweden	Brazil, Canada, China, Greece, Italy, Japan, Poland, Slovenia, Spain, Switzerland	13,100
		Carboxycyclophosphamide	Slovenia, Spain		
		Ketocyclophosphamide	Slovenia, Spain		
		N-dechloroethyl-cyclophosphamide	Slovenia, Spain		
	Gemcitabine	Parent	Canada	Brazil, Slovenia, Spain	750
	Cytarabine	Parent		Canada, Greece, Spain	924
	Ifosfamide	Parent	Canada, Slovenia	Germany, Spain, Switzerland	130.1

Matrix	Pharmaceutical	Analyte	Countries not found in	Countries detected in	Max conc. (ng/L)
Treated	Capecitabine	Parent	Slovenia, United Kingdom	Canada, Greece, Japan, Portugal, Spain	52.2
	Dacarbazine	Parent		Greece	84.8
	Imatinib	Parent		United Kingdom	301.7 (Average)
	Fluorouracil	Parent	Brazil, Canada, France, Slovenia, Switzerland, USA	Spain	< LOQ
		FBAL	Brazil		
	Methotrexate	Parent	Slovenia, Sweden, Tunisia, United Kingdom, USA	Canada, Greece, Italy, Jordan, Spain	332,000
		Hydroxymethotrexate	Slovenia, Spain		
	Cyclophosphamide	Parent	Finland, France, Norway, Sweden	Australia, Brazil, Canada, China, Germany, Greece, Italy, Japan, Poland, Portugal, Slovenia, Spain, Switzerland	791
		Carboxycyclophosphamide	Slovenia, Spain		
		Ketocyclophosphamide	Slovenia, Spain		
		N-dechloroethyl-cyclophosphamide	Slovenia, Spain		
	Gemcitabine	Parent	Canada, Slovenia	Brazil, Spain	420
	Cytarabine	Parent		Canada, Greece, Spain	349
	Bleomycin	Parent		United Kingdom	19
	Ifosfamide	Parent	Canada, Slovenia	Germany, Spain, Switzerland	2,900

Data summarised from Appendix Table 14. FBAL, alpha-fluoro-beta-alanine; LOQ, limit of quantification.

Table 6 Summary of studies assessing presence of 21 target cytotoxic drugs in hospital wastewater

Pharmaceutical	Analyte	Countries not found in	Countries detected in	Max conc. (ng/L)
Capecitabine	Parent		Canada, Spain, Slovenia, Turkey	1,749
Fluorouracil	Parent	Brazil, Canada	Austria, France, Slovenia, Spain, Switzerland	122,000
	FBAL		Brazil	18,200
Methotrexate	Parent		Canada, China, Jordan, Slovenia, Spain, Tunisia	835,000
	Hydroxymethotrexate		Slovenia, Spain	846
Cyclophosphamide	Parent	Saudi Arabia	Brazil, Canada, China, France, Germany, Norway, Slovenia, Spain, Switzerland, Turkey	29,100
	Carboxycyclophosphamide	Spain	Slovenia	60,600
	Ketocyclophosphamide	Spain	Slovenia	1,340
	N-dechloroethyl-cyclophosphamide	Spain	Slovenia	5,520
Gemcitabine	Parent	Slovenia, Spain	Brazil, Canada, Switzerland	25,900
Cytarabine	Parent	Canada		
Ifosfamide	Parent		Canada, China, Germany, Slovenia, Spain	86,200

Data summarised from Appendix Table 15. FBAL, alpha-fluoro-beta-alanine.

Table 7 Urinary and fecal excretion rates, terminal half-life and known metabolites of the 21 target drugs

Drug	Intact urinary excretion*	Intact fecal excretion*	Terminal half-life	Known metabolites
Hydroxycarbamide	50% (25 – 80%, 30% as urea)	No information identified	3 – 4 h	Urea, AHA
Pertuzumab	No information identified, but renal excretion noted to be very low (Cai et al 2021)	No information identified	11 – 22 days	No named metabolites identified
Capecitabine+	2.9% (84.2%, 57% as FBAL, 0.5% fluorouracil)	2.6%^	0.62 h	FU, 5'-DFCR, 5'-DFUR, DHFU, FUPA, FBAL
Dacarbazine	20 – 50% (12 – 24% as AIC)	No information identified	5 h	MTIC, AIC
Imatinib	13%^	68%^	18 h	N-desmethyl derivative (CGP 74588)
Fluorouracil	< 10%	No information identified	8 – 14 min (IV bolus)	FdUMP, FUTP, FdUTP, DHFU
Alectinib	< 0.5%	84% (98%, 6% as M4)	32.5 h	M4
Mercaptopurine	(7 - 40%)	No information identified	90 min	TUA, 6-MMP, thiopurine nucleotides
Venetoclax	<0.1%	20.8% (>99.9%)	26 h	M27
Methotrexate	80 – 90%	10%	3 – 15h	MTX polyglutamates, 7-OH MTX, DAMPA
Nilotinib	None	69% (93%)	15 – 17 h	No named metabolites identified
Palbociclib	6.9% (17.5%)	2.3% (74.1%)	29 h	Glucuronide and sulfamic acid conjugates
Cyclophosphamide	5 – 25%	31-66% after oral dose^	1.8 – 12.4h	4-OHCP, AP, PDA, ACR, 4-keto CP, CPM, NOR
Nintedanib#	0.05% (0.65%)	20% (93.4%)	10 – 15 h	m4, m7, m8, BIBF1202, BIBF1053, BIBF1202 1-*O*-acylglucuronide
Pazopanib	< 4%	60 – 70% (67 – 85%)	31 h	No named metabolites identified
Gemcitabine	<10% (92 – 98%, 89% as dFdU)	No information identified	0.7 – 10.6 h	dFdCDP, dFdCTP, dFdU
Cytarabine	10% (70 – 80%, 90% of which as Ara-U)	No information identified	1 – 4 h	Ara-U, Ara-CTP
Olaparib	(44%)	(42%)	11.9 h	No named metabolites identified
Bleomycin	60 – 70%	No information identified	2 – 5 h	No named metabolites identified
Ifosfamide	14 – 50% (15 – 41% as metabolites)	No information identified	4 – 8 h (11 – 15 h for high dose)	PDA, ACR
Dasatinib	0.1% (<4%)	19% (85%)	5 – 6h	BMS 582691

Terminal half-life refers to “the time required to divide the plasma concentration by two after reaching pseudo-equilibrium” (Toutain & Bousquet-Mélou 2004). ^Unclear if unchanged or total excretion. *Values in brackets indicate total amount including metabolites and parent drug, unless stated otherwise. +Judson et al (1999). #Wind et al (2019). AHA, acetohydroxamic acid; FU, fluorouracil; 5’-DFCR, 5′-deoxy-5-fluorocytidine; 5’-DFUR, 5'-deoxy-5-fluorouridine; DHFU dihydrofluorouracil; FUPA, α-fluoro-β-ureido propionic acid; FBAL, α-fluoro-β-alanine; MTIC, methyltriazenoimidazole carboxamide; AIC, aminoimidazole carboxamide; FdUMP, 5-fluorodeoxyuridine monophosphate; FUTP, 5- fluorouridine triphosphate; FdUTP, 5-fluoro-2′-deoxyuridine 5′-triphosphate; TUA, 6-thiouric acid; 6-MMP, 6-methylmercaptopurine; MTX, methotrexate; 7-OH MTX, 7-hydroxymethotrexate; DAMPA, 4-amino-4-deoxy-N10-methylpteroic acid; 4-OHCP, 4-hydroxycyclophosphamide; AP, aldophosphamide; PDA, phosphoramide mustard; ACR, acrolein; 4-keto CP, 4-keto-cyclophosphamide; CPM, carboxyphosphamide; NOR, nornitrogen mustard; dFdCDP, gemcitabine diphosphate; dFdCTP, gemcitabine triphosphate; dFdU, difluorodeoxyuridine; Ara-U, uracil arabinoside; Ara-CTP, cytarabine triphosphate. Data obtained from the following sources, accessed 20 April 2023: http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Hydroxyurea_monograph_1Oct2013.pdf, last updated 1 October 2013; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Pertuzumab_monograph.pdf, last updated 1 December 2021; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Dacarbazine_monograph_1June2013_formatted.pdf, last updated 1 June 2013; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Imatinib_Monograph_1Mar2017.pdf, last updated 1 March 2017; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil_monograph.pdf, last updated 1 September 2022; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Alectinib_monograph.pdf last updated 1 May 2019; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Mercaptopurine_monograph.pdf, last updated 1 April 2018; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Venetoclax_monograph.pdf last updated 1 August 2022; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Methotrexate_monograph.pdf, last updated 1 October 2022; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Nilotinib_monograph_1Mar2017.pdf last updated 1 March 2017; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Palbociclib_monograph.pdf, last updated 1 September 2020; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cyclophosphamide_monograph_1June2013_formatted.pdf, last updated 1 June 2013; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Pazopanib_monograph_1Oct2015.pdf last updated 1 October 2015; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Gemcitabine_monograph.pdf last updated 1 August 2021; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cytarabine%20monograph.pdf, last updated 1 May 2023; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Olaparib_monograph.pdf, last updated 1 June 2022; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Bleomycin_monograph_1Dec2014.pdf, last updated 1 December 2014; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Ifosfamide_monograph_1June2010_formatted.pdf, last updated 1 June 2010; http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Dasatinib_monograph_1Mar2017.pdf last updated 1 March 2017.

Table 8 Biodegradability of the target drugs

Drug	Biodegradability tests					Predicted % intact drug after WWTP biodegradation*	Estimated half-life in water (days)#
	Test	Incubation (days)	Initial conc. (ng/L)	% degraded	Reference		
Hydroxycarbamide						5.0	
Capecitabine	AS incubation	2		100% (in 24h)	Franquet-Griell et al (2017b)	85.0	60
	AS incubation	11	1,000,000	> 99%	Kosjek et al (2013)		
Dacarbazine						98.2	
Imatinib	Modified ZWT	7	1,000,000	100%	Tkalec et al (2021)	98.2	180
Fluorouracil	Laboratory-scale STP	10	5,000,000, 10,000,000, 20,000,000	100 ± 4%	Kiffmeyer et al (1998)	85.0	60
	CBT	40	9,020,000	0%	Kümmerer and Al-Ahmad (1997)		
	Modified ZWT	7	854,000,000	2%	Kümmerer and Al-Ahmad (1997)		
	AS incubation	50	1,000, 50,000	~ 30 – 50%	Yu et al (2006)		
	AS incubation	40 h	1,000,000	> 99%	Kosjek et al (2013)		
	AS incubation	1	5,000, 500,000	95 – 98%	Mahnik et al (2007)		
Methotrexate	Laboratory-scale STP	10	10,000,000, 20,000,000	98 ± 6%	Kiffmeyer et al (1998)	90.0	180
	CBT	28		44 ± 3%	Lutterbeck et al (2015)		
	Manometric respiration test	28		Not readily degradable	Henschel et al (1997)		
Nilotinib						84.5	

Drug	Biodegradability tests					Predicted % intact drug after WWTP biodegradation*	Estimated half-life in water (days)#
	Test	Incubation (days)	Initial conc. (ng/L)	% degraded	Reference		
Cyclophosphamide	AS incubation	2		15% (in 24 h)	Franquet-Griell et al (2017b)	98.1	38
	AS incubation	1	90 900	0%	Buerge et al (2006)		
	Laboratory-scale STP	10	375,000,000, 750,000,000	0 ± 5%	Kiffmeyer et al (1998)		
	ZWT	28	160,000,000	0%	Steger-Hartmann et al (1997)		
	Laboratory-scale STP	39	10,000	17%	Steger-Hartmann et al (1997)		
Pazopanib						89.4	
Gemcitabine	AS incubation	2		100% (in 15 min)	Franquet-Griell et al (2017b)	70.0	38
	CBT	28	7,000,000	42%	Kümmerer and Al-Ahmad (1997)		
	Modified ZWT	7	1,660,000,000	50%	Kümmerer and Al-Ahmad (1997)		
Cytarabine	Laboratory-scale STP	10	12,500,000, 25,000,000	60 ± 8%	Kiffmeyer et al (1998)	90.0	60
	AS incubation	2		100% (in 24 h)	Franquet-Griell et al (2017b)		
	CBT	40	4,500,000	85%	Kümmerer and Al-Ahmad (1997)		
	Modified ZWT	7	228,000,000	> 95%	Kümmerer and Al-Ahmad (1997)		
Bleomycin						100	180
Ifosfamide	AS incubation	2		15% (in 24 h)	Franquet-Griell et al (2017b)	98.1	180
	Modified ZWT	42	5,000,000, 160,000,000	0%	Kümmerer et al (1997)		
	Laboratory-scale STP	56	11,400	<3%	Kümmerer et al (1997)		

AS, activated sludge; ZWT, Zahn-Wellens test; CBT, closed bottle test. *From Booker et al (2014). #From Castellano-Hinojosa et al (2023).

3.3.1 Hydroxycarbamide

Hydroxycarbamide (Figure 3), or hydroxyurea, is a hydroxylated molecule of urea[36] approved in New Zealand for myeloproliferative neoplasms[37]. This drug exerts its toxicity by interfering with DNA synthesis via several different mechanisms, including blocking of ribonucleotide reductase which prevents conversion of ribonucleotides to deoxyribonucleotides, and inhibition of incorporation of thymidine into DNA[38]. It may also directly damage DNA[39].

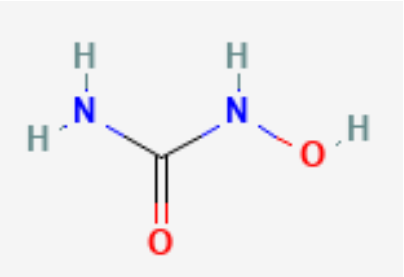

Figure 3 Structure of hydroxycarbamide

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/3657

During 2022 over 680 kg of hydroxycarbamide was estimated to have dispensed in around 32,000 dispensings (including repeat dispensings), making this the most highly dispensed cytotoxic drug in New Zealand in 2022 terms of mass (based on community dispensing data) (Table 1).

It has been estimated that up to 50% of administered hydroxycarbamide is excreted unchanged in urine, but no information on excretion in faeces was identified (Table 7). Assuming all the dispensed hydroxycarbamide was administered, based on an estimated 50% urinary excretion rate this would mean over 340 kg of hydroxycarbamide may have been discharged to New Zealand wastewater networks during 2022.

Little information on the biodegradation of hydroxycarbamide was identified. However, it has been noted to decompose in the presence of moisture[40] and to have low stability in water (Musiałek & Rybaczek 2021). Additionally, Booker et al (2014) predicted only 5% of intact hydroxycarbamide would be intact after biodegradation. A Spanish study noted that hydroxycarbamide had a mean predicted environmental concentration (PEC) in WWTP effluents of 832 ng/L and a mean PEC in river water of 32 ng/L (Franquet-Griell et al 2015), implying this drug is not completely biodegraded.

[36] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Hydroxyurea_monograph_1Oct2013.pdf Accessed 13 February 2023
[37] https://www.nzf.org.nz/nzf_4969 Accessed 3 February 2023
[38] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Hydroxyurea_monograph_1Oct2013.pdf Accessed 3 February 2023
[39] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Hydroxyurea_monograph_1Oct2013.pdf Accessed 3 February 2023
[40] https://www.sigmaaldrich.com/deepweb/assets/sigmaaldrich/product/documents/978/199/h8627pis.pdf Accessed 13 February 2023

No studies specifically assessing the presence of hydroxycarbamide in wastewater were identified. However, it has been predicted to have a treatment removal rate of only 2% (Franquet-Griell et al 2015).

3.3.2 Pertuzumab

Pertuzumab is a recombinant humanized monoclonal antibody[41] approved in New Zealand for treatment of HER2-positive breast cancer[42]. This drug acts by blocking extracellular dimerization of the human epidermal growth factor receptor 2 protein (HER2) with other HER proteins, inhibiting ligand-initiated signalling leading to arrest of cell growth and apoptosis[43].

In 2022 an estimated 480 kg of Pertuzumab was dispensed in New Zealand in 2,800 dispensings. Very little information on excretion of Pertuzumab in urine or faeces could be identified. However, renal excretion of this drug is noted to be very low (Cai et al 2021).

No studies assessing the biodegradability of Pertuzumab, or its presence in wastewater, were identified during preparation of this report.

3.3.3 Capecitabine

Capecitabine (Figure 4) is an antimetabolite drug approved in New Zealand for treatment of breast, colon, colorectal and oesophago-gastric cancers[44]. This prodrug is converted to its active metabolite, fluorouracil, via three-steps, with the last step catalysed by thymidine phosphorylase, an enzyme whose levels are 3 – 10 times higher several solid tumours compared to adjacent normal tissues (Figure 5) (Walko & Lindley 2005). Fluorouracil then exerts its cytotoxicity as discussed in Section 3.3.6 above.

In 2022 over 370 kg of capecitabine was estimated to have been dispensed in around 11,500 dispensings (including repeat dispensings) (Table 1). It has been estimated that up to 84% of a capecitabine dose is excreted in urine as the parent drug and metabolites over 48 h (Judson et al 1999). However, only around 3% of this is unchanged capecitabine, 0.5% is fluorouracil and around 57% is the inactive metabolite FBAL[45] (Judson et al 1999). No information on excretion in faeces was identified. Assuming all the capecitabine dispensed in 2022 was administered, a 3% excretion rate would correspond to around 11 kg of capecitabine discharged to New Zealand wastewater networks.

[41] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Pertuzumab_monograph.pdf Accessed 21 April 2023
[42] https://www.nzf.org.nz/nzf_70065 Accessed 21 April 2023
[43] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Pertuzumab_monograph.pdf Accessed 21 April 2023
[44] https://www.nzf.org.nz/nzf_4529 Accessed 3 February 2023
[45] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Capecitabine_monograph.pdf Accessed 6 April 2023

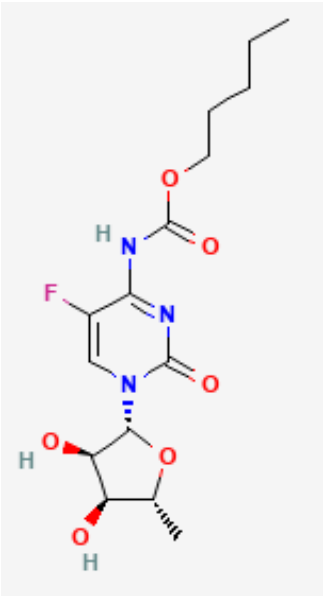

Figure 4 Structure of capecitabine

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/60953

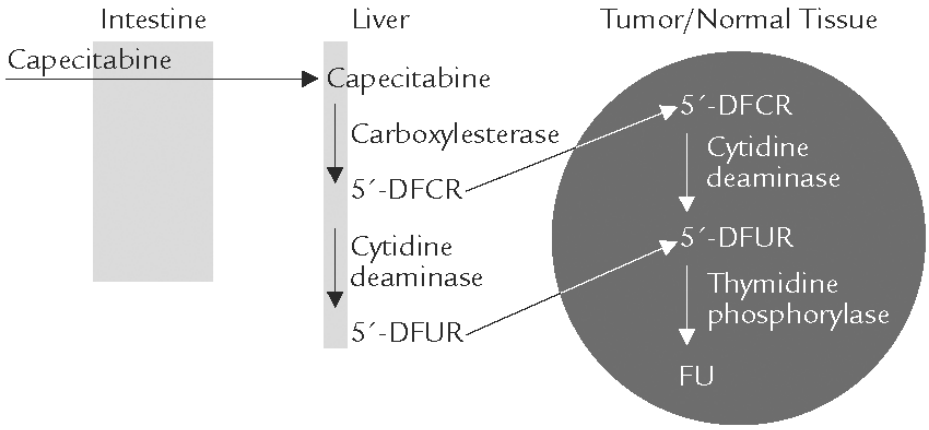

Figure 5 Metabolism of capecitabine to fluorouracil

Reproduced from Walko and Lindley (2005).

Two activated sludge incubation studies have shown that capecitabine is fully degraded within 24 h (Franquet-Griell et al 2017b) and 11 days (Kosjek et al 2013). However, Booker et al (2014) predicted that 85% of capecitabine reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that capecitabine has an estimated half-life in water of 60 days.

Capecitabine has been reported in municipal wastewater influents in Canada, Greece, Slovenia, Spain and the United Kingdom in concentrations up to 158 ng/L and in effluents in Canada, Greece, Japan, Portugal and Spain in concentrations up to 52.2 ng/L (Table 5). It has also been detected in hospital wastewaters in Canada, Spain, Slovenia and Turkey at

concentrations up to 1,749 ng/L (Table 6). Detection of capecitabine in wastewater effluents implies this drug is not always completely removed by treatment processes. Indeed, the removal efficiency for capecitabine by municipal wastewater plants was been predicted to only be around 15% (Besse et al 2012). Although, removal in two Greek WWTPs was 100% (Ofrydopoulou et al 2022).

3.3.4 Dacarbazine

Dacarbazine (Figure 6) is an alkylating agent approved in New Zealand for treatment of metastatic melanoma, soft tissue sarcomas and Hodgkin's disease[46].

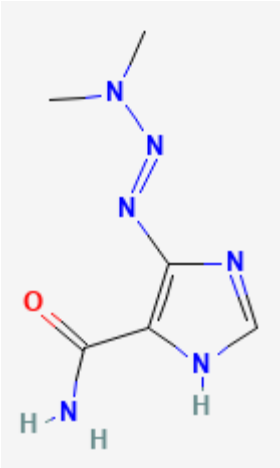

Figure 6 Structure of dacarbazine

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/135398738

In 2022, just over 80 kg of dacarbazine is estimated to have been dispensed in New Zealand in around 800 dispensings (Table 1). Between 20 – 50% of administered dacarbazine is excreted unchanged in urine, and between 12 – 24% is excreted as its inactive metabolite AIC[47]. Although no studies specifically assessing biodegradability of dacarbazine were identified, Booker et al (2014) predicted that 98.2% of dacarbazine reaching WWTPs would still be intact after biodegradation.

Dacarbazine has been identified in municipal wastewater in Greece, with concentrations of up to 1,124 ng/L in untreated wastewater and 84.8 ng/L in treated wastewater (Table 5). The removal efficiency in the two WWTPs assessed in this Greek study were 96 and 100% (Ofrydopoulou et al 2022), suggesting the majority of dacarbazine may be removed by wastewater treatment. However, given this drug could still be detected in treated wastewater it is obviously not always fully removed.

[46] https://www.nzf.org.nz/nzf_4610 Accessed 20 April 2023
[47] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Dacarbazine_monograph_1June2013_formatted.pdf Accessed 21 April 2023

3.3.5 Imatinib

Imatinib (Figure 7), also known as imatinib mesylate[48], is a protein kinase inhibitor approved in New Zealand for treatment of a range of different cancers[49]. This cytotoxic agent acts by inhibiting the BCR-ABL tyrosine kinase expressed in cancerous cells, leading to inhibition of growth or apoptosis[50].

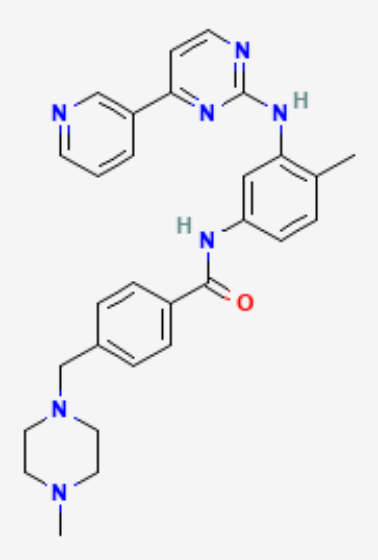

Figure 7 Structure of imatinib

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Imatinib

During 2022 around 67 kg of imatinib was estimated to have been dispensed in just over 3,700 dispensings (including repeat dispensings) (Table 1). Approximately 13% and 68% of administered imatinib is excreted unchanged and as metabolites in urine and faeces respectively[51]. Around 28% of the amount excreted corresponds to unchanged imatinib and 13% corresponds to its active metabolite CGP 74588 (Gschwind et al 2005).

Using a modified Zahn-Wellens biodegradation test, imatinib was found to be completely degraded within 7 days (Tkalec et al 2021). However, Booker et al (2014) predicted that 98.2% of imatinib reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that imatinib has an estimated half-life in water of 180 days.

Imatinib has been detected in both influent and effluent municipal wastewater in the United Kingdom (Proctor et al 2019, Rice et al 2020). In the study of Proctor et al (2019), imatinib concentrations increased in effluent compared to influent, possibly due to conjugated

[48] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Imatinib_Monograph_1Mar2017.pdf Accessed 14 February 2023
[49] https://www.nzf.org.nz/nzf_4674 Accessed 3 February 2023
[50] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Imatinib_Monograph_1Mar2017.pdf Accessed 3 February 2023
[51] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Imatinib_Monograph_1Mar2017.pdf Accessed 14 February 2023

metabolites present in wastewater being transformed back to the parent compound during treatment. The removal of imatinib from wastewater has predicted to only be around 6% (Franquet-Griell et al 2015).

3.3.6 Fluorouracil

Fluorouracil (Figure 13), also known as 5-fluorouracil or 5-FU[52], is an antimetabolite cytotoxic drug approved in New Zealand for various cancers including some gastro-intestinal, breast and skin cancers[53]. Fluorouracil is an analogue of uracil which acts as an antagonist of this pyrimidine[54]. This drug is metabolised to three active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine-5-triphosphate (FUTP)[55], as shown in Figure 9. The first of these, FdUMP acts by impairing DNA synthesis and repair by competing with uracil for binding to thymidylate synthetase, ultimately leading to reduced cell proliferation; FdUTP impairs DNA replication via incorporation into DNA; and FUTP impairs RNA processing and protein synthesis via incorporation into RNA[56].

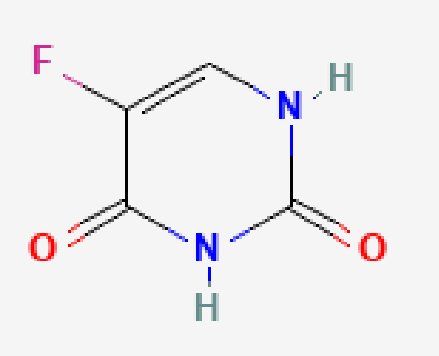

Figure 8 Structure of fluorouracil

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/3385

[52] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil_monograph.pdf Accessed 13 February 2023
[53] https://www.nzf.org.nz/nzf_4540 Accessed 3 February 2023
[54] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil_monograph.pdf Accessed 3 February 2023
[55] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil_monograph.pdf Accessed 3 February 2023
[56] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil_monograph.pdf Accessed 3 February 2023

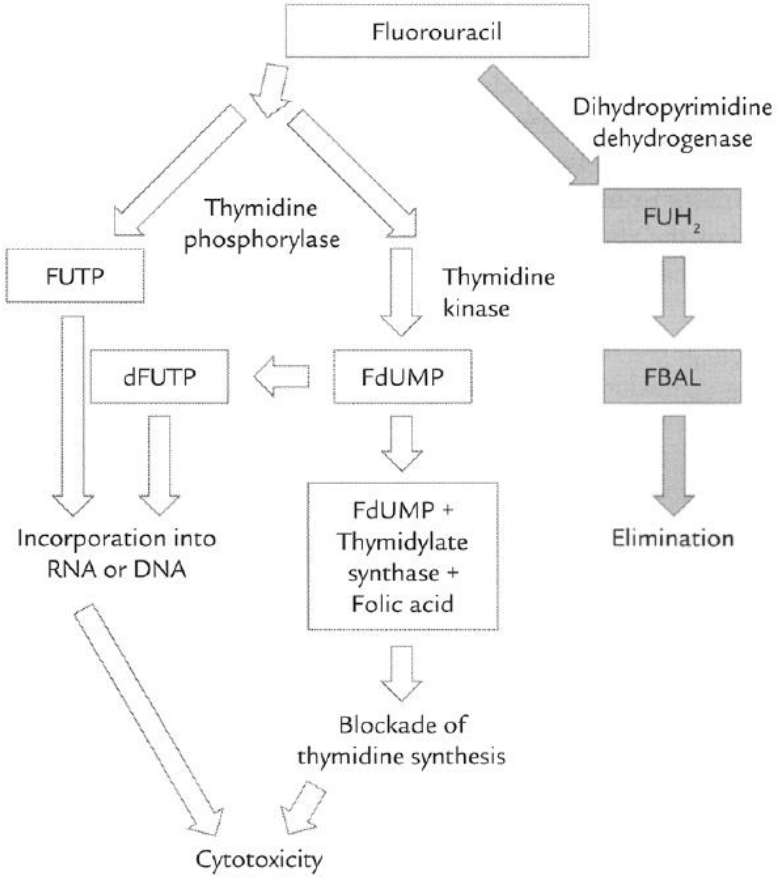

Figure 9 Metabolism of fluorouracil

Reproduced from Walko and Lindley (2005).

In 2022, fluorouracil was dispensed as both injectable formulations and as fluorouracil sodium cream. Around 60 kg of the injectable formulations and 82 kg of the cream are estimated to have been dispensed in 2022, in around 21,000 and 77,000 dispensings respectively (Table 1). Urinary excretion of fluorouracil is estimated to be less than 10%, and no information on fecal excretion was identified[57]. Importantly, this urinary excretion is not limited to intravenous administration as patients receiving topical fluorouracil treatment have also been shown to excrete this drug in their urine (Levy et al 2001), although it is estimated that only approximately 6% of a 5% topical fluorouracil cream application is absorbed systemically[58].

Fluorouracil is also formed by human metabolism of another cytotoxic drug capecitabine[59], which is also dispensed in relatively high amounts in New Zealand (Table 1), potentially adding to the load of fluorouracil reaching municipal WWTPs.

[57] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil_monograph.pdf Accessed 10 February 2023
[58] https://www.drugs.com/monograph/fluorouracil-topical.html Accessed 10 February 2023
[59] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Capecitabine_monograph.pdf Accessed 13 February 2023

Two studies assessing biodegradability of fluorouracil in activated sludge found almost 100% was degraded within 24 h (Mahnik et al 2007) to 40 h (Kosjek et al 2013). However, a third study found only around 30 – 50% was degraded after 50 days incubation (Yu et al 2006). Using a laboratory-scale sewage treatment plant, Kiffmeyer et al (1998) found complete degradation of fluorouracil within 10 days (Kiffmeyer et al 1998). However, Kümmerer and Al-Ahmad (1997) found using a Closed Bottle and Zahn-Wellens test that fluorouracil was not biodegradable. Additionally, capecitabine may undergo UV and microbial degradation to fluorouracil, although it appears to be considerably more persistent than fluorouracil (Kosjek et al 2013). Booker et al (2014) predicted that 85% of fluorouracil reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that fluorouracil has an estimated half-life in water of 60 days.

Of the ten studies that assessed the presence of fluorouracil in municipal wastewater, it was only detected in two, with a maximum concentration of 3.5 ng/L in untreated wastewater and < LOQ in treated wastewater (Table 14). In contrast, several studies identified fluorouracil in hospital effluents, at concentrations up to 122,000 ng/L (Table 15). The fluorouracil metabolite alpha-fluoro-beta-alanine (FBAL) has also been detected in influent municipal wastewater and hospital wastewater in Brazil at concentrations up to 13,500 and 18,200 ng/L respectively (de Oliveira Klein et al 2021). No studies assessing the presence of FdUMP, FdUTP or FUTP in wastewater were identified. The higher prevalence of fluorouracil in hospital compared to municipal effluents likely reflects the short terminal half-life of this drug of 8 – 14 min after an intravenous bolus[60], which is likely administered in a hospital setting.

3.3.7 Alectinib

Alectinib (Figure 13) is a protein kinase inhibitor approved in New Zealand for certain lung cancers[61]. This drug exerts its cytotoxicity by inducing tumour cell death through inhibition of anaplastic lymphoma kinase (ALK) phosphorylation, disrupting normal signalling[62]. It also inhibits cyclin-G-associated kinase (GAK) and leukocyte tyrosine kinase receptor (LTK)[63].

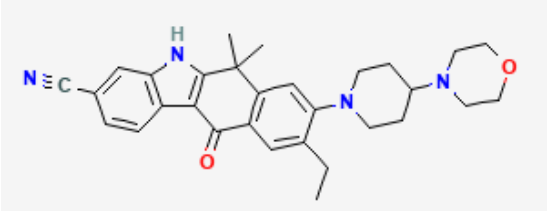

Figure 10 Structure of alectinib

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Alectinib

[60] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil_monograph.pdf Accessed 10 February 2023
[61] https://www.nzf.org.nz/nzf_70806 Accessed 8 February 2023
[62] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Alectinib_monograph.pdf Accessed 10 February 2023
[63] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Alectinib_monograph.pdf Accessed 10 February 2023

In 2022, around 25 kg of alectinib was estimated to have been dispensed in just under 700 dispensings (Table 1). Up to 98% of an alectinib dose is excreted in faeces, 84% unchanged[64]. Less than 0.5% is excreted in urine[65].

No studies assessing the presence of this drug in municipal or hospital wastewater, or its biodegradability, were identified during preparation of this report.

3.3.8 Mercaptopurine

Mercaptopurine (Figure 11), or 6-mercaptopurine[66], is an antimetabolite prodrug approved in New Zealand for treatment of certain leukaemias and severe acute Crohn's disease[67]. Mercaptopurine is an antagonist of purines which is activated *in vivo* via enzymatic conversion to thioinosine monophosphate (TIMP), which inhibits purine synthesis[68]. This metabolite is subsequently converted to thioguanine monophosphate (TGMP), then thioguanosine triphosphate (TGTP)[69]. These nucleotides then become incorporated into DNA in place of normal nucleotides, leading to cytotoxicity[70].

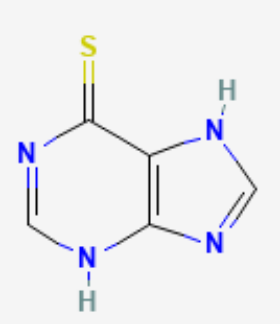

Figure 11 Structure of mercaptopurine

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/667490

In 2022, around 25 kg of mercaptopurine was estimated to have been dispensed in around 16,000 dispensings (including repeat dispensings) (Table 1).

[64] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Alectinib_monograph.pdf Accessed 10 February 2023
[65] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Alectinib_monograph.pdf Accessed 10 February 2023
[66] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Mercaptopurine_monograph.pdf Accessed 14 February 2023
[67] https://www.nzf.org.nz/nzf_4544 Accessed 3 February 2023
[68] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Mercaptopurine_monograph.pdf Accessed 3 February 2023
[69] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Mercaptopurine_monograph.pdf Accessed 3 February 2023
[70] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Mercaptopurine_monograph.pdf Accessed 3 February 2023

Between 7 – 40% of administered mercaptopurine is excreted in urine in its unchanged form and as metabolites, with low renal excretion at conventional doses and between 20 – 40% excretion at high doses[71]. No information on excretion in faeces was identified.

No studies specifically assessing biodegradation of mercaptopurine were identified during preparation of this report. Although, it has been noted to have low biodegradability (González-Burciaga et al 2021). Additionally, no studies assessing the presence of mercaptopurine in wastewater were identified. However, the removal rate of mercaptopurine from wastewater has been predicted to only be around 2% (Franquet-Griell et al 2015).

3.3.9 Venetoclax

Venetoclax (Figure 13) is a cytotoxic drug approved in New Zealand for certain leukaemias and lymphomas[72]. Venetoclax is a small-molecule inhibitor which exerts its cytotoxicity by inhibiting the anti-apoptotic protein B-cell lymphoma 2 (BCL-2)[73].

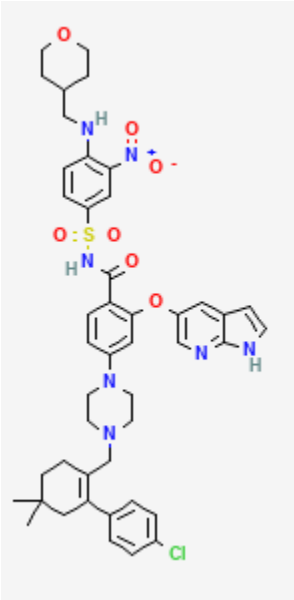

Figure 12 Structure of venetoclax

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Venetoclax

In 2022, around 23 kg of venetoclax is estimated to have been dispensed in New Zealand in just under 1,500 dispensings (Table 1). Venetoclax is primarily excreted in faeces, with more

[71] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Mercaptopurine_monograph.pdf Accessed 14 February 2023
[72] https://www.nzf.org.nz/nzf_70852 Accessed 8 February 2023
[73] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Venetoclax_monograph.pdf Accessed 8 February 2023

than 99.9% of an administered dose excreted via this route, 20.8% unchanged and the remainder as metabolites[74]. Less than 0.1% is estimated to be excreted in urine[75].

No studies assessing the presence of venetoclax in municipal or hospital wastewaters were identified during preparation of this report. Additionally, no information on its biodegradability was identified.

3.3.10 Methotrexate

Methotrexate (Figure 13), also known as amethopterim[76], is an antimetabolite cytotoxic drug approved in New Zealand for antineoplastic chemotherapy as well as some other non-cancer conditions as discussed in Section 2.3[77]. This drug acts as a folate antagonist, resulting in cytotoxicity due to inhibition of the enzymes dihydrofolate reductase and thymidylate, and by altering transport of reduced folates[78].

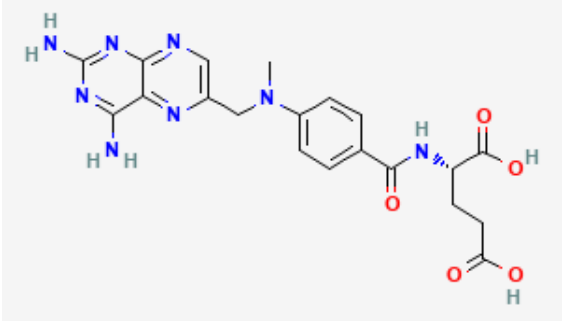

Figure 13 Structure of methotrexate

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/126941

In 2022 22 kg of methotrexate was estimated to have been dispensed in more than 165,000 dispensings (including repeat dispensings) (Table 1). Approximately 80 – 90% of administered methotrexate is excreted in urine, and around 10% is excreted in faeces, with metabolism of methotrexate estimated to be lower than 10%[79]. Assuming all the methotrexate dispensed in 2022 was administered, and assuming a 90% excretion rate, almost 20 kg of methotrexate may have been discharged to wastewater networks, spread out both temporally (across the year) and spatially (across the country).

[74] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Venetoclax_monograph.pdf Accessed 10 February 2023
[75] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Venetoclax_monograph.pdf Accessed 10 February 2023
[76] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Methotrexate_monograph.pdf Accessed 13 February 2023
[77] https://www.nzf.org.nz/nzf_4548 Accessed 3 February 2023
[78] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Methotrexate_monograph.pdf Accessed 2 February 2023
[79] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Methotrexate_monograph.pdf Accessed 2 February 2023

A 1998 study of the biodegradation of methotrexate in a laboratory-scale sewage treatment plant found that after 10 days around 98% was degraded (Kiffmeyer et al 1998). This study noted that by the second day of the test, the methotrexate metabolite 7-hydroxymethotrexate could be detected, with its concentration increasing at the same rate at which the methotrexate concentration decreased, suggesting 7-hydroxymethotrexate is not further biodegraded (Kiffmeyer et al 1998). Indeed, 7-hydroxymethotrexate does not appear to biodegrade and is considered persistent in water (Poirier Larabie et al 2022). This metabolite is also cytotoxic, but less so than methotrexate (Kiffmeyer et al 1998). However, in contrast to the results of Kiffmeyer et al (1998), biodegradability tests conducted by Henschel et al (1997) and Lutterbeck et al (2015) found that methotrexate was not readily biodegradable (Table 8). Supportive of this, Booker et al (2014) predicted that 90% of methotrexate reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that capecitabine has an estimated half-life in water of 180 days, suggesting this drug is highly stable and not readily biodegradable.

Methotrexate has been detected in influent and effluent municipal wastewater in several different countries, at concentrations up to 450,000 ng/L and 332,000 ng/L respectively (Table 5). It has also been detected in hospital wastewaters at concentrations up to 835,000 ng/L (Table 6).

Several studies have assessed removal of methotrexate by WWTPs. A 2010 Jordanian study found removal efficiencies of 25, 27 and 56% for three treatment plants (Alahmad & Alawi 2010). In contrast, removal efficiencies of 93 and 94% were found for two WWTPs in Greece (Ofrydopoulou et al 2022). A Canadian study found no significant difference between the concentrations of methotrexate in influent and effluent wastewater at three treatment plants, although they note that the plant residence time was very short (<3 h), meaning little time for biodegradation (Rabii et al 2014). Vaudreuil et al (2020) also note that their detection of methotrexate in municipal wastewater effluents implies that removal at the assessed treatment plants is not totally effective.

3.3.11 Nilotinib

Nilotinib (Figure 13) is a protein kinase inhibitor approved in New Zealand for certain leukaemias[80]. This drug exerts its cytotoxicity by inhibiting the Abl tyrosine kinase activity of the BCR-ABL oncoprotein, leading to inhibition of proliferation and induction of apoptosis[81].

In 2022, around 18 kg of nilotinib is estimated to have been dispensed in New Zealand in just under 900 dispensings (Table 1). Up to 93% of administered nilotinib is excreted in faeces, 69% as the unchanged parent drug, with no urinary excretion[82]. Given this high percentage of administered nilotinib excreted unchanged in faeces it could potentially be present in wastewaters reaching treatment plants. However, no studies assessing the presence of nilotinib in municipal or hospital wastewaters were identified during preparation of this report. Additionally, no information on the biodegradability of nilotinib was identified,

[80] https://www.nzf.org.nz/nzf_4678 Accessed 8 February 2023
[81] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Nilotinib_monograph_1Mar2017.pdf Accessed 10 February 2023
[82] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Nilotinib_monograph_1Mar2017.pdf Accessed 10 February 2023

with the exception of the report of Booker et al (2014) which predicted that 84.5% of nilotinib reaching WWTPs would still be intact after biodegradation.

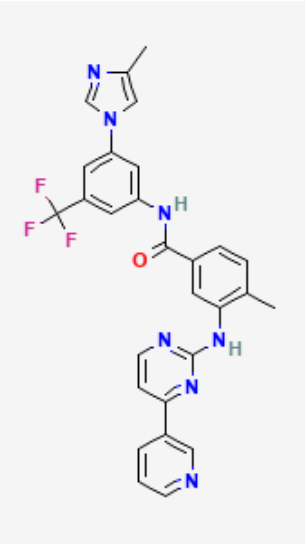

Figure 14 Structure of nilotinib

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Nilotinib

3.3.12 Palbociclib

Palbociclib (Figure 15) is a protein kinase inhibitor approved in New Zealand for treatment of certain breast cancers[83]. Palbociclib exerts its toxicity by inhibiting specific cyclin-dependent kinases, leading to inhibition of the cell cycle[84].

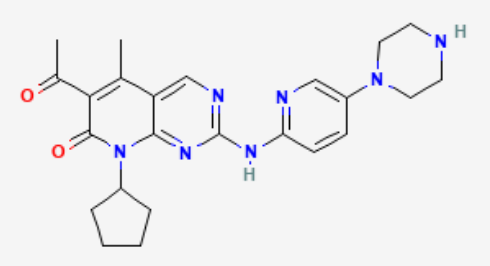

Figure 15 Structure of Palbociclib

Reproduced from https://pubchem.ncbi.nlm.nih.gov/compound/5330286

During 2022 around 17 kg of palbociclib was estimated to have been dispensed in New Zealand in around 7,300 dispensings (including repeat dispensings) (Table 1).

[83] https://www.nzf.org.nz/nzf_70757 Accessed 3 February 2023
[84] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Palbociclib_monograph.pdf Accessed 3 February 2023

Approximately 6.9% of administered palbociclib is excreted unchanged in urine and 2.3% in faeces[85].

No information on biodegradability of palbociclib, or its presence in wastewater, was identified during preparation of this report.

3.3.13 Cyclophosphamide

Cyclophosphamide (Figure 7) is an alkylating agent approved in New Zealand for treatment of some leukaemias, lymphomas and solid tumours, and for rheumatoid arthritis[86]. This prodrug is converted to a phosphoramide mustard *in vivo* via a cytochrome P450 enzyme (Ortiz de Montellano 2013). This phosphoramide mustard then spontaneously cyclizes to form an aziridinium DNA crosslinking agent (Ortiz de Montellano 2013), which causes toxicity due to crosslinking of DNA and RNA, and inhibition of protein synthesis[87].

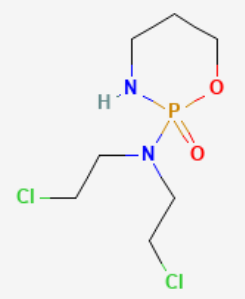

Figure 16 Structure of cyclophosphamide

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/2907

In 2022, almost 16 kg of cyclophosphamide was estimated to have been dispensed in New Zealand in just under 11,000 dispensings (Table 1). Estimates of the amount of administered cyclophosphamide excreted unchanged in urine vary slightly. According to the British Columbia Cancer drug monograph, 5 – 25% of administered cyclophosphamide is excreted unchanged in urine and 31 – 66% is excreted in faeces after an oral dosage[88]. Bagley et al (1973), found a maximum of 20% of an injected dose was excreted unchanged in urine, whereas Juma et al (1979) found 1.8 – 11.9% of administered cyclophosphamide was excreted unchanged, with no difference when administered orally or intravenously.

Several studies have assessed the biodegradability of cyclophosphamide. All these studies found that cyclophosphamide is not readily biodegradable, with degradation percentages

[85] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Palbociclib_monograph.pdf Accessed 14 February 2023
[86] https://www.nzf.org.nz/nzf_4453 Accessed 3 February 2023
[87] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cyclophosphamide_monograph_1June2013_formatted.pdf Accessed 3 February 2023
[88] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cyclophosphamide_monograph_1June2013_formatted.pdf Accessed 14 February 2023

ranging from 0 – 17%. However, Buerge et al (2006) noted that many of these studies were conducted using very high concentrations which may result in cytotoxic effects on the degrading microbes. To address this, they assessed biodegradability at much lower concentrations which could occur in WWTPs. However, even at these low concentrations there was no degradation within 24 h (Buerge et al 2006). Booker et al (2014) predicted that 98.1% of cyclophosphamide reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that cyclophosphamide has an estimated half-life in water of 38 days.

Cyclophosphamide has been identified in influent and effluent municipal wastewater around the world at concentrations up to 13,100 ng/L and 791 ng/L respectively (Table 5). It has also been detected in hospital wastewater at concentrations up to 29,100 ng/L (Table 6).

Several studies have assessed removal of cyclophosphamide from wastewater. Buerge et al (2006) found that levels of this drug were comparable between untreated and treated wastewater. Similarly, Ofrydopoulou et al (2022) found a removal efficiency of only 35% for a WWTP in Greece. Using a laboratory scale sewage treatment plant Steger-Hartmann et al (1997) found that cyclophosphamide was not readily removed, with 83% recoverable in the effluent. Additionally, Kovalova et al (2012) found less than 20% was removed from hospital wastewater using a membrane bioreactor. In contrast, Delgado et al (2011) achieved a removal efficiency of up to 80% using a crossflow membrane bioreactor (with a 48 h hydraulic retention time and 50 days solids retention time).

3.3.14 Nintedanib

Nintedanib (Figure 13) is a protein kinase inhibitor approved in New Zealand for certain lung cancers as well as idiopathic pulmonary fibrosis[89].

During 2022, around 14 kg of nintedanib was dispensed in just under 1,600 dispensings (including repeat dispensings) (Table 1).

Around 93.4% of administered nintedanib is excreted in faeces and 0.65% in urine unchanged and as metabolites[90]. Of this, approximately 20% is excreted unchanged and 59% is its major metabolite BIBF1202 (Wind et al 2019) (Figure 18).

No information on biodegradation of nintedanib or its presence in municipal or hospital wastewater were identified during preparation of this report.

[89] https://www.nzf.org.nz/nzf_70790 Accessed 8 February 2023
[90] https://www.drugs.com/monograph/nintedanib.html Accessed 14 February 2023

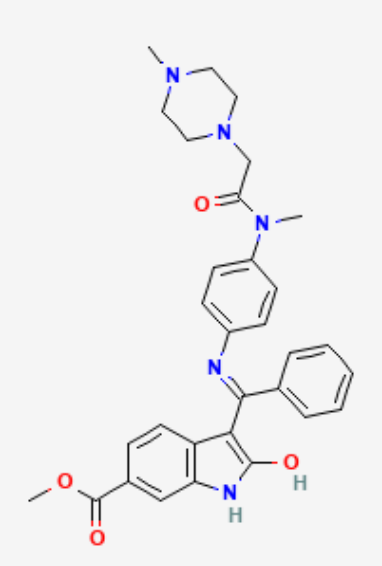

Figure 17 Structure of nintedanib

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Nintedanib

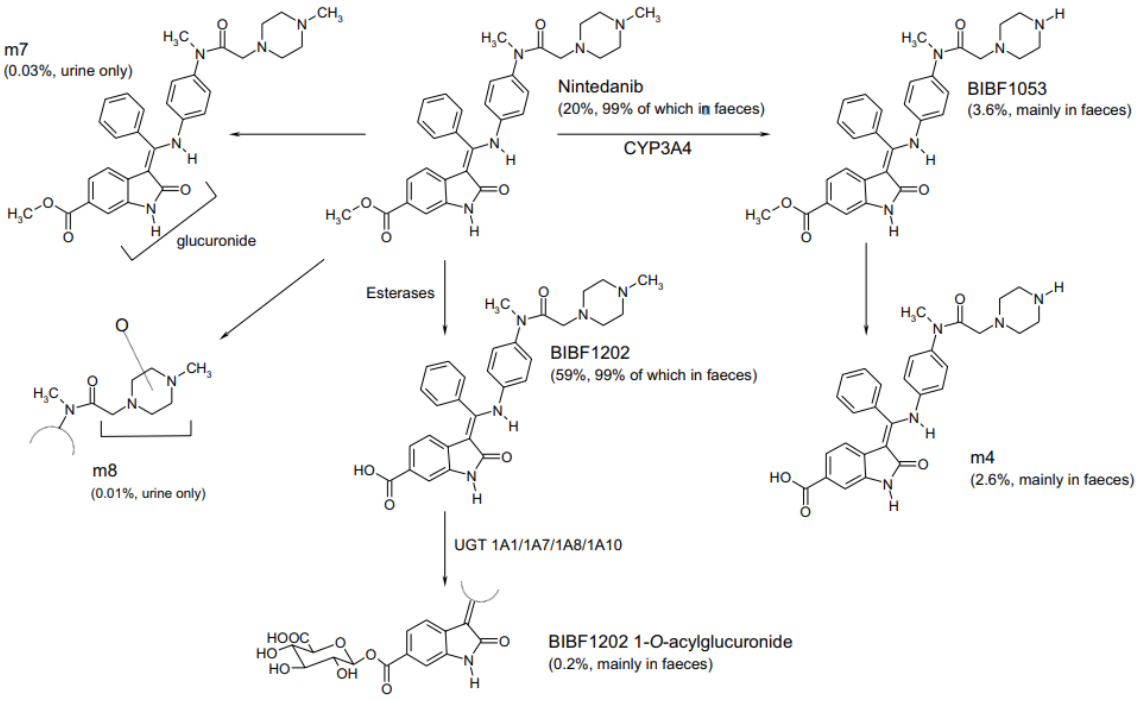

Figure 18 Metabolism and excretion of nintedanib

Reproduced from Wind et al (2019). Values in brackets are the percentages excreted as a proportion of the total dose.

3.3.15 Pazopanib

Pazopanib (Figure 13) is a protein kinase inhibitor approved in New Zealand for certain renal and soft-tissue cancers[91]. Pazopanib exerts its cytotoxicity by blocking tumour growth by interfering with angiogenesis (formation of new blood vessels) through inhibition of several target proteins including vascular endothelial growth factor receptor (VEGFR-1, -2, -3), platelet-derived growth factor receptor (PDGFR-α, -β), and stem cell factor receptor (c-KIT)[92]. It also inhibits fibroblast growth factor receptor (FGFR-1 and -3), interleukin receptor (IL-2), and the transmembrane glycoprotein receptor tyrosine kinase (c-Fms)[93].

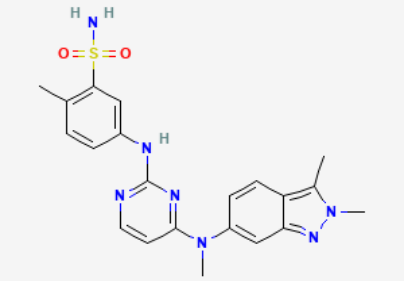

Figure 19 Structure of pazopanib

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Pazopanib

In 2022, an estimated 13.5 kg of pazopanib was dispensed in New Zealand in almost 800 dispensings (Table 1). Pazopanib is primarily excreted in faeces, with 60-70% excreted unchanged and 7-15% excreted as metabolites, and less than 4% excreted in urine [94]. Given the large percentage of administered pazopanib excreted unchanged in faeces it could potentially be present in wastewaters reaching treatment plants. However, no studies assessing the presence of pazopanib in municipal or hospital wastewater, or its biodegradability, were identified during preparation of this report, with the exception of the study of Booker et al (2014) which predicted that 89.4% of pazopanib reaching WWTPs would still be intact after biodegradation.

3.3.16 Gemcitabine

Gemcitabine (Figure 20), also known as gemcitabine hydrochloride[95], is an antimetabolite cytotoxic drug agent approved in New Zealand for treatment of a range of different cancers[96]. This drug is an analogue of pyrimidine which is metabolised to two active

[91] https://www.nzf.org.nz/nzf_4680 Accessed 8 February 2023
[92] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Pazopanib_monograph_1Oct2015.pdf Accessed 10 February 2023
[93] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Pazopanib_monograph_1Oct2015.pdf Accessed 10 February 2023
[94] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Pazopanib_monograph_1Oct2015.pdf Accessed 10 February 2023
[95] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Gemcitabine_monograph.pdf Accessed 20 April 2023
[96] https://www.nzf.org.nz/nzf_4542 Accessed 20 April 2023

metabolites – gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP)[97]. The cytotoxicity of gemcitabine occurs through incorporation of dFdCTP into DNA, aided by dFdCDP, inhibiting DNA synthesis and inducing apoptosis[98].

In 2022, 9.5 kg of gemcitabine was estimated to have been dispensed in New Zealand, in around 5,500 dispensings (Table 1). Gemcitabine is mainly excreted in urine, although less than 10% is estimated to be excreted intact, with 89% excreted as its inactive metabolite difluorodeoxyuridine (dFdU)[99].

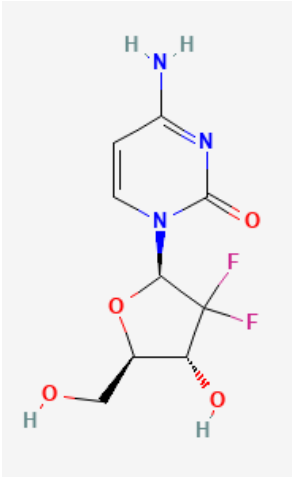

Figure 20 Structure of gemcitabine

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/60750

Several studies have assessed the biodegradability of gemcitabine. Franquet-Griell et al (2017b) found that gemcitabine was completely degraded within 15 minutes in their activated sludge incubation experiment. In contrast, Kümmerer and Al-Ahmad (1997) found only 42% and 50% was degraded in a closed bottle test and modified Zahn-Wellens test respectively. Booker et al (2014) predicted that 70% of gemcitabine reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that gemcitabine has an estimated half-life in water of 38 days.

Gemcitabine has been detected in untreated municipal wastewater in Brazil, Slovenia and Spain at concentrations up to 750 ng/L, and in treated wastewater in Brazil and Spain at concentrations up to 420 ng/L (Table 5). It has also been detected in hospital wastewater in Brazil, Canada and Switzerland at concentrations up to 25,900 ng/L (Table 6).

[97] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Gemcitabine_monograph.pdf Accessed 21 April 2023
[98] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Gemcitabine_monograph.pdf Accessed 21 April 2023
[99] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Gemcitabine_monograph.pdf Accessed 21 April 2023

3.3.17 Cytarabine

Cytarabine (Figure 21) is an antimetabolite cytotoxic drug agent approved in New Zealand for treatment of certain leukaemias[100]. Cytarabine is a synthetic pyrimidine nucleoside[101] and is structurally similar to gemcitabine[102]. Cytarabine is metabolised to cytarabine triphosphate (Ara-CTP) which competes with deoxycytidine triphosphate, resulting in inhibition of DNA synthesis[103]. Its cytotoxicity may also be enhanced by its incorporation into DNA and RNA[104].

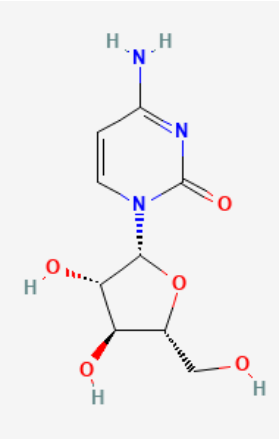

Figure 21 Structure of cytarabine

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/6253

In 2022, almost 9 kg of cytarabine was estimated to have been dispensed in New Zealand, in around 1,700 dispensings (Table 1). Around 70 – 80% of administered cytarabine is excreted in urine, 10% as the intact drug and 90% as its inactive metabolite uracil arabinoside (Ara-U)[105].

Several studies have assessed the biodegradability of cytarabine. Franquet-Griell et al (2017b) found that cytarabine was completely degraded within 24 hours in their activated sludge incubation experiment. Kümmerer and Al-Ahmad (1997) found 85% and >95% was degraded in a closed bottle test and modified Zahn-Wellens test respectively. In contrast, Kiffmeyer et al (1998) found only around 60% was degraded using a laboratory-scale sewage treatment plant. Booker et al (2014) predicted that 90% of cytarabine reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that cytarabine has an estimated half-life in water of 60 days.

[100] https://www.nzf.org.nz/nzf_4535 Accessed 20 April 2023
[101] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cytarabine%20monograph.pdf Accessed 21 April 2023
[102] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Gemcitabine_monograph.pdf Accessed 21 April 2023
[103] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cytarabine%20monograph.pdf Accessed 4 May 2023
[104] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cytarabine%20monograph.pdf Accessed 4 May 2023
[105] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cytarabine%20monograph.pdf Accessed 4 May 2023

Cytarabine has been detected in untreated and treated municipal wastewater in Canada, Greece and Spain at concentrations up to 924 ng/L (untreated) and 349 ng/L (treated) (Table 5). Although assessed in hospital wastewater in Canada it was not detected (Vaudreuil et al 2020).

3.3.18 Olaparib

Olaparib (Figure 22) is a cytotoxic drug approved in New Zealand for treatment of several different cancers[106]. This drug acts as a selective inhibitor of poly (ADP-ribose) polymerases (PARPs)[107]. Olaparib binds to PARPs leading to inhibition of normal DNA repair and causing double-stranded DNA breaks, leading to the death of tumour cells unable to repair double-stranded breaks[108].

In 2022, 8 kg of olaparib was estimated to have been dispensed in New Zealand, in around 500 dispensings (Table 1). Olaparib is excreted in both urine and faeces, with around 44% excreted in urine and 42% excreted in faeces as the intact drug and its metabolites[109].

No studies specifically addressing biodegradation of Olaparib were identified during preparation of this report, but AstraZeneca have noted that it is 'not readily biodegradable[110]. Additionally, no studies assessing the presence of this drug in wastewater were identified.

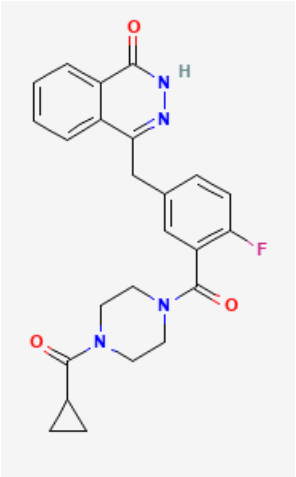

Figure 22 Structure of olaparib

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/23725625

[106] https://www.nzf.org.nz/nzf_70534 Accessed 21 April 2023
[107] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Olaparib_monograph.pdf Accessed 21 April 2023
[108] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Olaparib_monograph.pdf Accessed 21 April 2023
[109] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Olaparib_monograph.pdf Accessed 21 April 2023
[110] https://www.astrazeneca.com/content/dam/az/our-company/Sustainability/Olaparib.pdf Accessed 21 April 2023

3.3.19 Bleomycin

Bleomycin sulfate (Figure 23), often referred to simply as bleomycin[111], is a cytotoxic glycopeptide antibiotic approved in New Zealand for treatment of several different types of cancers[112]. This drug exerts its cytotoxicity by causing DNA breakage through formation of a free radical complex, leading to inhibition of DNA synthesis (and to a lesser extent RNA and protein synthesis)[113, 114].

In 2022, just over 6 kg of bleomycin was estimated to have been dispensed in New Zealand, in around 800 dispensings (Table 1). Around 60 – 70% of administered bleomycin is estimated to be excreted unchanged in urine[115].

No studies directly assessing biodegradation of bleomycin were identified. However, Booker et al (2014) predicted that 100% of bleomycin reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that bleomycin has an estimated half-life in water of 180 days, suggesting this drug is highly stable and not readily biodegradable.

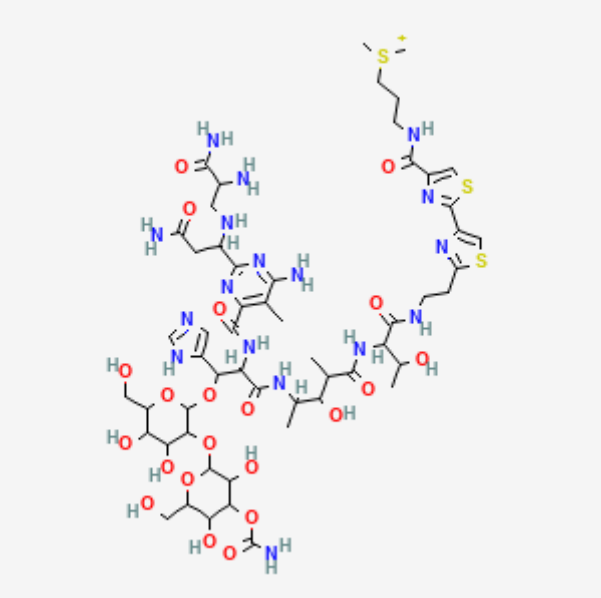

Figure 23 Structure of bleomycin

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/72466

Bleomycin has been detected in treated municipal wastewater in the United Kingdom at concentrations up to 19 ng/L (Aherne et al 1990).

[111] https://pubchem.ncbi.nlm.nih.gov/compound/Bleomycin-sulfate Accessed 21 April 2023
[112] https://www.nzf.org.nz/nzf_4480 Accessed 21 April 2023
[113] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Bleomycin_monograph_1Dec2014.pdf Accessed 21 April 2023
[114] https://www.nzf.org.nz/nzf_4480 Accessed 21 April 2023
[115] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Bleomycin_monograph_1Dec2014.pdf Accessed 21 April 2023

3.3.20 Ifosfamide

Ifosfamide (Figure 24) is an alkylating agent approved in New Zealand for treatment of some solid tumours, sarcomas and lymphomas[116]. This drug exerts its cytotoxicity through formation of phosphotriesters and DNA-DNA crosslinks, which result in inhibition of DNA, RNA and protein synthesis[117, 118].

In 2022, around 6 kg of ifosfamide was estimated to have been dispensed in New Zealand, in almost 1,100 dispensings (Table 1). Between 14 – 50% of administered ifosfamide is estimated to be excreted unchanged in urine, and a further 15 – 41% is estimated to be excreted in urine as ifosfamide metabolites[119].

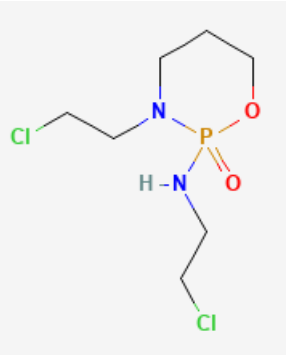

Figure 24 Structure of ifosfamide

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/3690

Several studies have assessed the biodegradability of ifosfamide. Franquet-Griell et al (2017b) found that only 15% was degraded after 24 hours in activated sludge, and Kümmerer et al (1997) found little (< 3%) to no degradation using a laboratory-scale sewage treatment plant and modified Zahn-Wellens test. Booker et al (2014) predicted that 98.1% of ifosfamide reaching WWTPs would still be intact after biodegradation, and a review by Castellano-Hinojosa et al (2023) noted that ifosfamide has an estimated half-life in water of 180 days. Overall, these studies suggest ifosfamide is not readily biodegradable.

Ifosfamide has been detected in untreated and treated municipal wastewater in Germany, Spain and Switzerland at concentrations up to 130.1 ng/L (untreated) and 2,900 (treated) (Table 5). It has also been detected in hospital wastewater in Canada, China, Germany, Slovenia and Spain at concentrations up to 86,200 ng/L (Table 6).

[116] https://www.nzf.org.nz/nzf_4458 Accessed 21 April 2023
[117] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Ifosfamide_monograph_1June2010_formatted.pdf Accessed 21 April 2023
[118] https://www.nzf.org.nz/nzf_4458 Accessed 21 April 2023
[119] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Ifosfamide_monograph_1June2010_formatted.pdf Accessed 21 April 2023

3.3.21 Dasatinib

Dasatinib (Figure 13) is a protein kinase inhibitor approved in New Zealand for certain leukaemias[120]. Dasatinib exerts its cytotoxicity by inhibiting multiple tyrosine kinases including BCR-ABL, leading to disruption of normal cellular signalling[121].

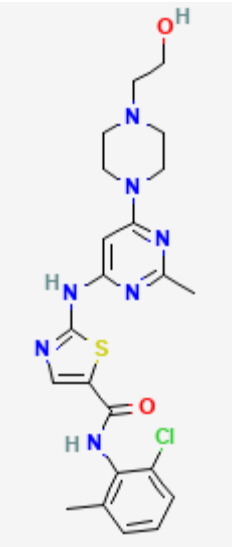

Figure 25 Structure of dasatinib

Reproduced from PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Dasatinib

In 2022, just under 5 kg of dasatinib was estimated to have been dispensed in New Zealand in almost 1,700 dispensings (including repeat dispensings) (Table 1). Dasatinib is predominantly excreted in faeces, with around 85% of an administered dose excreted via this route, 19% unchanged[122]. Less than 4% is excreted in urine, with <1% unchanged[123].

Given around 20% of administered dasatinib is excreted unchanged in faeces it could potentially be present in wastewaters reaching treatment plants. However, no studies assessing the presence of dasatinib in municipal or hospital wastewaters were identified during preparation of this report. Additionally, no information on the biodegradability of dasatinib was identified. Furthermore, it is unclear whether dasatinib metabolites excreted in faeces possess cytotoxic activity and could therefore also pose a health hazard.

[120] https://www.nzf.org.nz/nzf_4666 Accessed 8 February 2023
[121] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Dasatinib_monograph_1Mar2017.pdf Accessed 8 February 2023
[122] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Dasatinib_monograph_1Mar2017.pdf Accessed 10 February 2023
[123] http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Dasatinib_monograph_1Mar2017.pdf Accessed 10 February 2023

4. CYTOTOXIC DRUGS IN AQUATIC ENVIRONMENTS

As noted above, cytotoxic drugs may enter aquatic environments in wastewater effluents or in leachate from solid waste which has been incorrectly disposed of. Exposure to these toxic chemicals can then occur during recreational usage of contaminated waterways (surface waters), or through contamination of drinking-water supplies, as indicated in Figure 26.

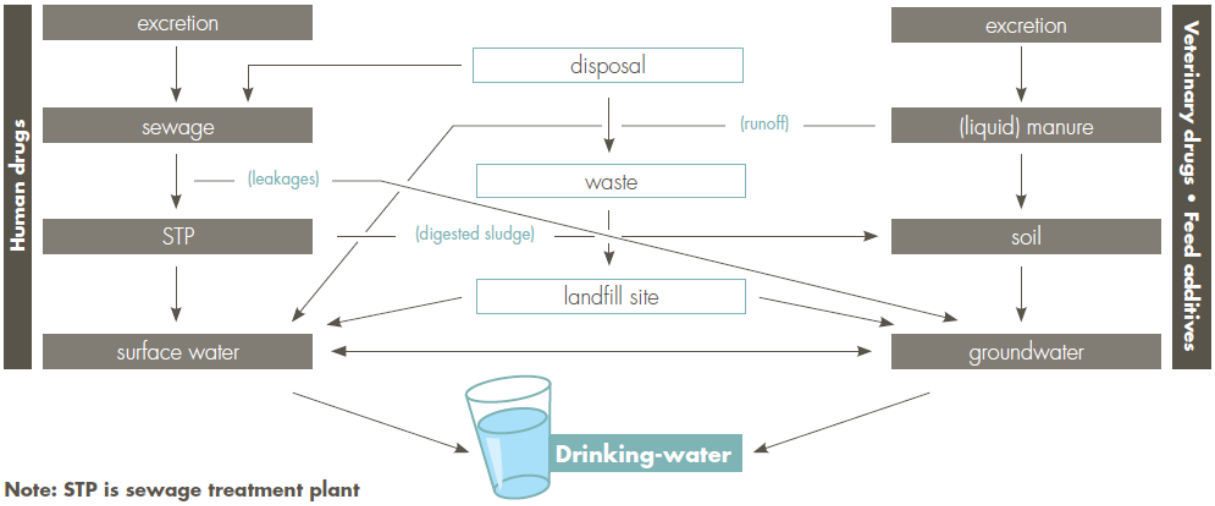

Figure 26 Fate of pharmaceuticals in the environment

Reproduced from WHO (2012).

Several cytotoxic drugs have been identified in surface-, ground- and drinking-water internationally, as summarised in Table 9. Those drugs which have been identified in these matrices include capecitabine, imatinib, methotrexate, cyclophosphamide, gemcitabine, cytarabine, bleomycin and ifosfamide. In New Zealand, Moreau et al (2019) conducted an assessment of emerging organic contaminants in groundwater which detected cyclophosphamide at one of nine targeted sites at a concentration of 6.4 ng/L. No information on the presence of the other target drugs in surface- or groundwater in New Zealand was identified.

In 2012 the World Health Organization published a Human health risk assessment for pharmaceuticals in drinking-water. This report notes that “health impacts to humans are very unlikely from exposure to the trace concentrations of pharmaceuticals that could potentially be found in drinking-water” (WHO 2012). However, they note that research into the potentially synergistic effects of pharmaceutical mixtures and potential risks to sensitive subpopulations would be beneficial for future risk assessments. At present there is insufficient information available to determine if cytotoxic drugs are present in ground- and/or surface-waters in New Zealand at levels which may pose a potential health hazard. Studies

assessing the presence of these drugs in wastewater effluent, as discussed above, will be able to guide the investigation in this area, as wastewater effluents are likely to be one of the most significant sources of cytotoxic drugs to these environments. If these studies identify cytotoxic drugs in wastewater effluents, then examination of the levels in surface- and/or groundwaters may be necessary.

Table 9 Summary of cytotoxic pharmaceuticals assessed in different aquatic matrices

Matrix	Pharmaceutical	Analyte	Countries not found in	Countries detected in	Max conc. (ng/L)
Surface waters (river, lake, other)	Capecitabine	Parent	Portugal, Spain, United Kingdom	Japan, Moldova	20
		2,3-di-O-acetyl-5-deoxy-5-fluorocytidine		Moldova	< LOQ
	Imatinib	Parent	Portugal	United Kingdom	183.3 (Average)
	Fluorouracil	Parent	Portugal, Slovenia, Spain		
	Methotrexate	Parent	Canada, Tunisia, United Kingdom	Spain, USA	161
	Cyclophosphamide	Parent	Australia, Belgium, Germany, Portugal	Canada, Italy, Japan, Moldova, Netherlands, Poland, Romania, Spain, Switzerland, Vietnam	64.8
	Gemcitabine	Parent		Moldova, Spain	2.4 (Average)
		2',2'-Difluoro-2'-deoxyuridine	Moldova		
	Cytarabine	Parent		Moldova, Spain	13 (Average)
	Bleomycin	Parent		United Kingdom	17
	Ifosfamide	Parent	Germany	Spain, Switzerland	41
Drinking water	Methotrexate	Parent	France, USA		
	Cyclophosphamide	Parent	France, Italy, Poland	Canada, China, Netherlands	1,233
	Gemcitabine	Parent	France		
	Bleomycin	Parent		United Kingdom	13
	Ifosfamide	Parent	France		

Matrix	Pharmaceutical	Analyte	Countries not found in	Countries detected in	Max conc. (ng/L)
Groundwater	Methotrexate	Parent		USA	14
	Cyclophosphamide	Parent		New Zealand	6.4

*183.3 ng/L was the average concentration.

5. SUMMARY

Although pharmaceuticals are designed to treat human disease and illness, unintentional exposure to these chemicals in the environment can pose a health hazard, particularly for sensitive subpopulations (eg, pregnant women, children, people with drug allergies). Cytotoxic pharmaceuticals, in particular, may pose a serious health hazard due to the highly toxic nature of these drugs.

Cytotoxic drugs act on rapidly dividing cells to interrupt cell replication, inhibit DNA synthesis and damage cellular DNA, and are well-known treatments for cancer and some autoimmune disorders. Some of these drugs have been identified in a range of aquatic environments including wastewater, surface-, ground- and drinking-water.

The aim of this report was to determine whether cytotoxic drugs are likely to be present in the environment in New Zealand and pose a potential health hazard. The first step in this assessment was to identify what cytotoxic drugs are used in New Zealand, and which are the most highly dispensed based on community dispensing data.

Over 60 different cytotoxic drugs were dispensed by community pharmacies in 2022. For 21 of these drugs, 5 kg or more (by mass not potency) was dispensed annually during these two years. These drugs were:

- Hydroxycarbamide
- Imatinib
- Venetoclax
- Cyclophosphamide
- Cytarabine
- Dasatinib
- Pertuzumab
- Fluorouracil
- Methotrexate
- Nintedanib
- Olaparib
- Capecitabine
- Alectinib
- Nilotinib
- Pazopanib
- Bleomycin
- Dacarbazine
- Mercaptopurine
- Palbociclib
- Gemcitabine
- Ifosfamide

These 21 drugs were selected as target drugs for further assessment in this report.

To determine whether these 21 target drugs were likely to be present in wastewater and could therefore pose a health hazard, information on their excretion in urine and/or faeces, biodegradability, detection in municipal or hospital wastewater, and removal from wastewater was assessed. These data are summarised in Table 10, together with the estimated mass dispensed in 2022.

For 20 of these drugs information showing their excretion in urine and/or faeces was identified. Capecitabine, dacarbazine, imatinib, fluorouracil, methotrexate, cyclophosphamide, gemcitabine, cytarabine, bleomycin and ifosfamide have all been detected in municipal wastewater effluents internationally, so it is possible they may also be present in effluents in New Zealand and any risk should therefore be investigated through an exposure assessment.

For the remaining 11 drugs (hydroxycarbamide, pertuzumab, alectinib, mercaptopurine, venetoclax, nilotinib, palbociclib, nintedanib, pazopanib, olaparib and dasatinib) no studies assessing their biodegradability or presence in wastewater were identified. Thus, to fully

assess the potential health hazard posed by these drugs, studies assessing their presence in wastewater in New Zealand are needed.

A preliminary assessment of the potential presence of these target drugs in other aquatic environments (eg, ground-, surface- and drinking-waters) was also undertaken. Capecitabine, imatinib, methotrexate, cyclophosphamide, gemcitabine, cytarabine, bleomycin and ifosfamide were found to have been detected in surface waters internationally. Methotrexate and cyclophosphamide have also been detected in groundwater, and cyclophosphamide and bleomycin have been detected in drinking water.

Only one study assessing the presence of these drugs in these aquatic matrices in New Zealand was identified. This study assessed the presence of a wide range of contaminants in groundwater but of the 21 target drugs in this report only cyclophosphamide was analysed and was only detected it in 1/9 targeted groundwater sampling sites. Future assessment of the presence of the target cytotoxic drugs in these aquatic matrices should be guided by studies assessing their presence in wastewater. If a target drug is detected in wastewater effluents, then assessment of its potential presence in these other environments may be warranted.

Table 10 Summary of excretion, biodegradability, presence and removal from wastewater for the 21 target drugs

Drug	Mass dispensed 2022 (kg)	% excreted unchanged in urine/faeces	Readily biodegradable	Detected in wastewater			Predicted % intact drug after WWTP biodegradation*
				Municipal influent	Municipal effluent	Hospital	
Hydroxycarbamide	686.9	50/ND	ND	ND	ND	ND	5
Pertuzumab	480.8	ND	ND	ND	ND	ND	ND
Capecitabine	371.4	2.9/2.6^	✓	✓	✓	✓	85
Dacarbazine	81.6	20 – 50/ND	ND	✓	✓	ND	98
Imatinib	67.6	13^/68^	✓	✓	✓	ND	98
Fluorouracil	81.5 FU sodium 59.3 FU	<10/ND	✓/✗	✓	✓	✓	85
Alectinib	24.6	<0.5/84	ND	ND	ND	ND	ND
Mercaptopurine	24.6	7 – 40#/ND	ND	ND	ND	ND	ND
Venetoclax	23.4	<0.1/20.8	ND	ND	ND	ND	ND
Methotrexate	22	80 – 90/10	✓/✗	✓	✓	✓	90
Nilotinib	17.6	0/69	ND	ND	ND	ND	85
Palbociclib	17.3	6.9/2.3	ND	ND	ND	ND	ND
Cyclophosphamide	15.6	5 – 25/31 – 66	✗	✓	✓	✓	98
Nintedanib	14.1	0.05/20	ND	ND	ND	ND	ND
Pazopanib	13.5	<4/60 – 70	ND	ND	ND	ND	90
Gemcitabine	9.5	<10/ND	✓/✗	✓	✓	✓	70
Cytarabine	8.8	10/ND	✓/✗	✓	✓	✗	90
Olaparib	8	44#/42#	ND	ND	ND	ND	ND
Bleomycin	6.4	60 – 70/ND	ND	ND	✓	ND	100
Ifosfamide	6.1	14 – 50/ND	✗	✓	✓	✓	98
Dasatinib	4.9	0.1/19	ND	ND	ND	ND	ND

ND, not determined or no information available; ✓/✗ indicates conflicting data from multiple studies. +Based on mass dispensed in 2022 x estimated maximum % excreted in urine and faeces based on identified information; *From Booker et al (2014); ^unclear if unchanged or total excretion; #as parent and metabolites.

APPENDIX

Table 11 Cytotoxic drugs dispensed in New Zealand 2017 – 2022

Drug	2022		2021		2020		2019		2018		2017	
	Total	Initial	Total	Initial	Total	Initial	Total	Initial	Total	Initial	Total	Initial
Acalabrutinib												
Afatinib												
Alectinib	665	304	631	281	549	251	38	30				
Arsenic trioxide	388	388	410	410	551	551	425	425	221	221	317	317
Atezolizumab												
Axitinib												
Azacitidine	4998	4998	5701	5701	5577	5577	5808	5808	5528	5528	4165	4165
Bendamustine HCl	2111	2111	3060	3060	2346	2346	2464	2464	2442	2442	782	782
Bevacizumab												
Bleomycin sulfate	828	828	976	976	909	909	926	926	1079	1079	899	899
Bortezomib	9156	9156	9595	9595	8819	8819	8533	8533	8330	8330	8652	8652
Busulfan	374	233	404	216	372	206	355	207	379	207	418	240
Capecitabine	11584	9777	11867	10101	11802	10249	13127	11480	13284	11628	12193	10753
Carboplatin	8080	8080	7926	7926	7182	7182	6562	6562	6369	6369	6151	6151
Carfilzomib												
Carmustine	60	60	88	88	77	77	77	77	72	72	64	64
Cetuximab	58	58	71	71	101	101	224	224	247	247		
Chlorambucil	550	434	634	477	620	468	669	515	713	572	764	587
Chlormethine HCl												
Cisplatin	3322	3322	3447	3447	3473	3473	3175	3175	3405	3405	3427	3427
Cladribine	76	76	64	64	105	105	74	74	55	55	88	88
Clofarabine												
Cobimetinib												
Crisantaspase												
Crizotinib												

Drug	2022		2021		2020		2019		2018		2017	
	Total	Initial	Total	Initial	Total	Initial	Total	Initial	Total	Initial	Total	Initial
Cyclophosphamide	10952	9578	11439	10212	11513	10138	11330	10091	10770	9752	10618	9667
Cytarabine	1699	1699	1844	1844	1939	1939	2214	2214	2144	2144	1998	1998
Dabrafenib												
Dacarbazine	798	798	951	951	932	932	761	761	1042	1042	823	823
Dactinomycin	131	131	149	149	146	146	143	143	157	157	162	162
Dasatinib	1656	693	1801	781	1812	805	1743	726	1878	809	1755	638
Daunorubicin	355	355	407	407	474	474	440	440	406	406	438	438
Docetaxel	4031	4031	4179	4179	3752	3752	4085	4085	4036	4036	3855	3855
Doxorubicin hydrochloride	5954	5954	6567	6567	6357	6357	6109	6109	6119	6119	6265	6265
Durvalumab	168	168										
Epirubicin HCl	1300	1300	1393	1393	1488	1488	1595	1595	2126	2126	2584	2584
Erlotinib	897	403	950	453	1123	540	1091	542	1107	542	1073	542
Etoposide	1088	928	1010	887	1164	1068	1289	1188	1788	1647	4855	4768
Etoposide phosphate	3315	3315	3363	3363	3118	3118	3248	3248	2678	2678	1042	1042
Everolimus	83	46	101	52	92	37	92	41	77	38	38	20
Fludarabine phosphate	374	354	509	479	513	477	605	578	498	489	651	617
Fluorouracil	20701	20701	22550	22550	22521	22521	20130	20130	18336	18336	20075	20075
Fluorouracil sodium	76731	72461	72975	68766	67379	63192	67175	63583	60384	57459	56788	54115
Gefitinib	495	226	602	255	608	279	608	263	654	295	636	273
Gemcitabine HCl	5545	5545	5687	5687	5521	5521	5054	5054	4998	4998	5729	5729
Gemtuzumab ozogamicin	20	20										
Hydroxycarbamide	32434	12734	31612	12201	29558	11449	27369	10910	25993	10103	23798	9298
Ibrutinib	<12	<12										
Idarubicin HCl	82	82	139	139	76	76	136	136	124	124	150	150
Ifosfamide	1072	1072	1198	1198	1056	1056	929	929	807	807	736	736
Imatinib mesilate	3727	2254	3386	2128	3654	1957	3039	1802	3241	1949	3226	1900

Drug	2022		2021		2020		2019		2018		2017	
	Total	Initial	Total	Initial	Total	Initial	Total	Initial	Total	Initial	Total	Initial
Ipilimumab												
Irinotecan HCl	5579	5579	6159	6159	5882	5882	4655	4655	4189	4189	4524	4524
Lenvatinib												
Lomustine	301	292	229	210	242	231	224	220	142	135	146	143
Melphalan	404	378	432	398	445	409	439	407	612	560	689	646
Mercaptopurine	15599	6372	15541	6266	14551	5933	13538	5695	12787	5478	12229	5376
Methotrexate	165706	111333	161045	107949	184470	102181	133600	96112	127554	91497	121613	87532
Mitomycin C	594	594	598	598	617	617	588	588	311	311	389	389
Mitoxantrone	108	108	85	85	107	107	157	157	96	96	162	162
Neratinib												
Nilotinib	891	373	837	361	840	342	788	320	751	310	640	269
Nintedanib	1585	662	1255	522	876	368	496	234	49	24		
Nivolumab	138	138	53	53	118	118	329	329	579	579	724	724
Olaparib	533	260	314	153	208	118						
Osimertinib												
Oxaliplatin	7476	7476	7939	7939	7555	7555	7588	7588	6216	6216	6074	6074
Paclitaxel	10577	10577	9844	9844	8794	8794	9197	9197	8557	8557	9696	9696
Palbociclib	7265	3867	6806	3805	4271	2695						
Pazopanib	799	351	709	325	552	249	644	316	716	371	770	388
Pembrolizumab	4040	4040	4240	4240	4196	4196	4944	4944	3701	3701	2707	2707
Pemetrexed	2178	2178	1861	1861	1821	1821	2078	2078	1662	1662	99	99
Pertuzumab	2800	2800	2695	2695	2494	2494	2175	2175	1695	1695	1031	1031
Procarbazine HCl	477	407	448	378	314	276	237	214	252	217	260	231
Ramucirumab												
Ribociclib												
Ruxolitinib	2262	937	1870	770	1301	566	939	449	156	104		
Sorafenib												
Sunitinib	998	635	991	630	1068	731	783	523	783	534	919	664
Temozolomide	3127	2386	2728	1968	2275	1828	2543	1872	2601	2017	3070	2115
Tioguanine												

Drug	2022		2021		2020		2019		2018		2017	
	Total	Initial	Total	Initial	Total	Initial	Total	Initial	Total	Initial	Total	Initial
Topotecan												
Trametinib												
Trastuzumab	8181	8181	8654	8654	8053	8053	8396	8396	8764	8764	8814	8814
Trastuzumab emtansine	1050	1050	964	964	822	822	39	39				
Tretinoin	35099	35083	29196	29171	26789	26771	25509	25500	24279	24270	22854	22846
Vemurafenib												
Venetoclax	1452	669	1281	641	631	387	<16	<16				
Vinblastine sulfate	1344	1344	1322	1322	1258	1258	1039	1039	1331	1331	1244	1244
Vincristine sulfate	4983	4983	5019	5019	4913	4913	5118	5118	5004	5004	5529	5529
Vinorelbine	2362	2362	2308	2308	2026	2026	2928	2928	2538	2538	2592	2592
Vismodegib												

List obtained from the New Zealand Formulary[124], does not include Section 29 unapproved medicines. Dispensing data obtained from Te Whatu Ora community dispensing database, excludes drugs not funded by the New Zealand Government[125].

[124] https://www.nzf.org.nz/nzf_4381 Accessed 31 January 2023
[125] https://www.tewhatuora.govt.nz/our-health-system/data-and-statistics/pharmaceutical-data-web-tool/ Accessed 9 February 2023

Table 12 Chemical formulations of the 21 target cytotoxic drugs dispensed during 2021 and/or 2022

Drug	Form	Volume/amount
Hydroxycarbamide	Capsule	500 mg
Pertuzumab	Injection	1 mg for ECP 420 mg for ECP 30 mg per ml, 14 ml vial
Capecitabine	Tablet	150 mg 500 mg
Dacarbazine	Injection	200 mg vial 200 mg for ECP
Imatinib mesilate	Capsule Tablet	100 mg 400 mg 100 mg
Fluorouracil	Injection	1 mg for ECP 50 mg per ml, 20 ml vial 50 mg per ml, 50 ml vial 50 mg per ml, 100 ml vial
Fluorouracil sodium	Cream	5%
Alectinib	Capsule	150 mg
Mercaptopurine	Oral suspension Tablet	20 mg per ml 50 mg
Venetoclax	Tablet	10 mg 50 mg 100 mg 14 x 10 mg, 7 x 50 mg, 21 x 100 mg

Drug	Form	Volume/amount
Methotrexate	Tablet Injection	2.5 mg 10 mg 1 mg for ECP 5 mg intrathecal syringe for ECP 7.5 mg prefilled syringe 10 mg prefilled syringe 15 mg prefilled syringe 20 mg prefilled syringe 25 mg prefilled syringe 30 mg prefilled syringe 2.5 mg per ml, 2 ml 25 mg per ml, 2 ml vial 25 mg per ml, 20 ml vial 100 mg per ml, 10 ml 100 mg per ml, 50 ml vial
Nilotinib	Capsule	150 mg 200 mg
Palbociclib	Capsule Tablet	75 mg 100 mg 125 mg 75 mg 100 mg 125 mg
Cyclophosphamide	Tablet Injection	50 mg 1 mg for ECP 1 g vial 2g vial
Nintedanib	Capsule	100 mg 150 mg

Drug	Form	Volume/amount
Pazopanib	Tablet	200 mg 400 mg
Gemcitabine	Injection	1 mg for ECP 200 mg 1 g 1 g, 26.3 ml vial
Cytarabine	Injection	1 mg for ECP 100 mg intrathecal syringe for ECP 20 mg per ml, 5 ml vial 100 mg per ml, 10 ml vial 100 mg per ml, 20 ml vial
Olaparib	Capsule Tablet	50 mg 100 mg 150 mg
Bleomycin sulfate	Injection	1,000 iu for ECP 15,000 iu vial
Ifosfamide	Injection	1 mg for ECP 1 g 2 g
Dasatinib	Tablet	20 mg 50 mg 70 mg

Data obtained from the Te Whatu Ora Pharmaceutical Collection on request. ECP, extracorporeal photopheresis; iu, international units.

Table 13 Amount (kg) of cytotoxic pharmaceuticals dispensed in New Zealand 2017 – 2022

Drug	2022	2021	2020	2019	2018	2017
Alectinib	***24.6***	***22.5***	***19.9***	1.4		
Arsenic trioxide	0.06	0.05	0.05	0.03	0.01	0.01
Azacitidine	0.9	0.9	0.8	0.7	0.7	0.5
Bendamustine HCl	0.4	0.5	0.4	0.4	0.4	0.1
Bleomycin sulfate[#]	***6.4***	***6.0***	***6.5***	***5.5***	***7.3***	***6.4***
Bortezomib	0.04	0.04	0.03	0.03	0.02	0.02
Busulfan	0.02	0.02	0.02	0.02	0.02	0.02
Capecitabine	***371.4***	***389.0***	***393.6***	***446.6***	***455.6***	***406.6***
Carboplatin	4.1	4.2	3.7	3.4	3.3	3.0
Carmustine	1.8	2.7	2.6	2.4	2.5	1.8
Cetuximab	0.02	0.04	0.04	0.1	0.1	
Chlorambucil	0.04	0.05	0.05	0.05	0.06	0.06
Cisplatin	0.4	0.4	0.4	0.3	0.4	0.3
Cladribine	0.02	0.02	0.02	0.02	0.01	0.02
Cyclophosphamide	***15.6***	***16.7***	***17.3***	***17.4***	***16.3***	***16.0***
Cytarabine	***8.8***	***9.0***	***7.7***	***8.1***	***7.2***	***7.8***
Dacarbazine	***81.6***	***90.4***	***86.6***	***75.6***	***98.0***	***63.8***
Dactinomycin	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Dasatinib	4.9	***5.4***	***5.5***	***5.1***	***5.1***	4.8
Daunorubicin	0.4	0.5	0.5	0.4	0.4	0.5
Docetaxel	0.5	0.6	0.5	0.5	0.5	0.5
Doxorubicin HCl	0.5	0.5	0.5	0.5	0.4	0.4
Durvalumab	0.3					
Epirubicin HCl	0.2	0.2	0.2	0.2	0.2	0.2
Erlotinib	3.5	3.8	4.4	4.5	4.7	4.8
Etoposide	0.7	0.7	0.7	0.7	1.0	1.6
Etoposide phosphate	1.3	1.4	1.2	1.2	1.0	0.3
Everolimus	0.02	0.02	0.02	0.02	0.02	0.01
Fludarabine phosphate	0.8	1.3	0.9	1.1	0.8	0.8
Fluorouracil	***59.3***	***62.9***	***61.6***	***52.7***	***45.2***	***44.0***

Drug	2022	2021	2020	2019	2018	2017
Fluorouracil sodium	81.5	78.4	71.8	71.8	64.0	59.5
Gefitinib	4.1	4.8	4.9	4.8	***5.3***	***5.0***
Gemcitabine HCl	***9.5***	***10.0***	***9.8***	***9.0***	***8.8***	***9.6***
Gemtuzumab ozogamicin	<0.02					
Hydroxycarbamide	***686.9***	***658.8***	***633.5***	***600.8***	***565.2***	***517.6***
Ibrutinib	0.04					
Idarubicin HCl	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Ifosfamide	***6.1***	***6.1***	***5.2***	4.8	4.5	3.3
Imatinib mesilate	***67.6***	***64.1***	***58.8***	***56.7***	***59.5***	***59.8***
Irinotecan HCl	1.7	1.9	1.7	1.4	1.3	1.3
Lomustine	0.04	0.03	0.03	0.03	0.02	0.02
Melphalan	0.08	0.1	0.09	0.08	0.09	0.09
Mercaptopurine	***24.6***	***24.2***	***23.0***	***22.2***	***21.2***	***20.7***
Methotrexate	***22.0***	***22.9***	***20.7***	***20.4***	***19.2***	***18.6***
Mitomycin C	<0.01	0.01	0.01	0.01	0.01	0.01
Mitoxantrone	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Nilotinib	***17.6***	***16.8***	***16.2***	***15.3***	***14.8***	***13.4***
Nintedanib	***14.1***	***11.2***	***7.8***	4.5	0.4	
Nivolumab	0.04	0.02	0.03	0.06	0.1	0.1
Olaparib	***8.0***	4.4	3.3			
Oxaliplatin	1.3	1.4	1.3	1.3	1.1	1.0
Paclitaxel	1.7	1.6	1.4	1.4	1.4	1.4
Palbociclib	***17.3***	***16.6***	***10.8***			
Pazopanib	***13.5***	***11.9***	***10.4***	***12.3***	***14.6***	***13.9***
Pembrolizumab	0.9	0.9	0.9	0.8	0.6	0.4
Pemetrexed	1.9	1.6	1.6	1.8	1.4	0.1
Pertuzumab	***480.8***	***338.5***	***230.0***	***180.6***	***46.0***	0.5
Procarbazine HCl	0.6	0.6	0.4	0.3	0.4	0.4
Ruxolitinib	1.7	1.4	1.0	0.8	0.1	
Sunitinib	0.8	0.8	0.9	0.7	0.7	0.8

Drug	2022	2021	2020	2019	2018	2017
Temozolomide	3.2	2.8	2.3	2.5	2.5	2.7
Trastuzumab	3.9	4.1	3.8	3.9	4.1	4.0
Trastuzumab emtansine	0.3	0.2	0.2	0.01		
Tretinoin	1.0	0.9	0.8	0.8	0.7	0.7
Venetoclax	***23.4***	***21.9***	***14.4***	1.1		
Vinblastine sulfate	0.01	0.01	0.01	0.01	0.01	0.01
Vincristine sulfate	0.01	0.01	0.01	0.01	0.01	0.01
Vinorelbine	2.3	0.8	0.08	0.1	0.1	0.1

Data obtained from the Te Whatu Ora Pharmaceutical Collection on request. Includes initial and repeat dispensings. Grey shading indicates non dispensed. Drugs with more than 5 kg dispensed are indicated in bold italics. [#]Amount is provided in international units (iu). Amount in kg estimated based on 1,500 iu = 1 mg (Stefanou 2001).

Table 14 International studies assessing presence of target cytotoxic drugs in municipal wastewater

Untreated wastewater				
Drug	**Target analyte**	**Country**	**Concentration (ng/L)**	**Reference**
Capecitabine	Parent	Canada	4.18 ± 0.41 – 64.4 ± 0.2	Vaudreuil et al (2020)
		Greece	ND – 59.4	Ofrydopoulou et al (2022)
		Slovenia	ND – 158 ± 13	Isidori et al (2016)
		Spain	< LOQ – 27.0	Negreira et al (2013)
			ND	Gómez-Canela et al (2014)
			< LOQ – 72.6	Negreira et al (2014a)
			ND	Isidori et al (2016)
		United Kingdom	ND – 13.3	Proctor et al (2019)
Dacarbazine	Parent	Greece	ND – 1124.0	Ofrydopoulou et al (2022)
Imatinib	Parent	United Kingdom	ND – 115.3	Proctor et al (2019)
			368.3 (average conc.)	Rice et al (2020)
Fluorouracil	Parent	Brazil	ND	de Oliveira Klein et al (2021)
		Canada	ND	Vaudreuil et al (2020)
		France	ND	Mullot et al (2010)
		Slovenia	ND – 14	Kosjek et al (2013)
			ND – 3.1 ± 0.4	Isidori et al (2016)
		Spain	ND	Martín et al (2011)
			ND	Martín et al (2014)
			< LOQ – 3.5 ± 0.5	Isidori et al (2016)
		Switzerland	ND	Tauxe-Wuersch (2005)
		USA	ND	Yu et al (2006)
			ND	Yu et al (2012)
	FBAL	Brazil	ND – 13,500	de Oliveira Klein et al (2021)

Drug	Target analyte	Country	Concentration (ng/L)	Reference
Methotrexate	Parent	Canada	ND – 59	Garcia-Ac et al (2009)
			< LOQ – 60	Rabii et al (2014)
			4.34 ± 0.33 – 27.3 ± 2.8	Vaudreuil et al (2020)
		China	1.6 – 18.1	Yin et al (2010b)
		Greece	ND – 433.2	Ofrydopoulou et al (2022)
		Jordan	100,000 ± 7,000 – 450,000 ± 6,000	Alahmad and Alawi (2010)
		Slovenia	29 ± 1 – 303 ± 5	Isidori et al (2016)
		Spain	ND	Martín et al (2011)
			2.1 – 20.1	Negreira et al (2013)
			< LOQ – 23 ± 2	Ferrando-Climent et al (2014)
			ND – 55.8	Martín et al (2014)
			ND – 18.1	Negreira et al (2014a)
			8.3 ± 1.3 – 29 ± 2	Isidori et al (2016)
		Spain/France/Portugal	< LOQ – 23.0 ± 0.4	Ferrando-Climent et al (2013)
		Sweden	ND	Li et al (2018)
		Tunisia	ND	Afsa et al (2020)
		United Kingdom	ND	Petrie et al (2016)
			ND	Proctor et al (2019)
	Hydroxymethotrexate	Slovenia	ND – 366 ± 35	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)

Drug	Target analyte	Country	Concentration (ng/L)	Reference
Cyclophosphamide	Parent	Brazil	ND – < LOQ	de Oliveira Klein et al (2021)
		Canada	ND – 9	Garcia-Ac et al (2009)
			ND – 22	Rabii et al (2014)
			ND – 118 ± 3	Vaudreuil et al (2020)
		China	ND – 69.8	Sun et al (2016)
		France	ND	Miossec et al (2019)
			ND	Mullot et al (2010)
		Greece	ND – 12	Ofrydopoulou et al (2022)
		Italy	ND – 220	Morosini et al (2017)
		Japan	2.8	Kadokami and Ueno (2019)
		Norway	ND	Thomas et al (2007)
		Poland	ND – 33.3	Kot-Wasik et al (2016)
		Slovenia	ND – 27 ± 7.3	Česen et al (2015)
			ND	Česen et al (2016)
			19 ± 3 – 27 ± 7	Isidori et al (2016)
		Spain	ND	Martín et al (2011)
			ND – 13,100	Gómez-Canela et al (2012)
			ND - 10	Gómez-Canela et al (2014)
			8 ± 0.2 – 26 ± 2	Ferrando-Climent et al (2014)
			ND	Martín et al (2014)
			ND – 43.8	Negreira et al (2014a)
			ND – 6.0 ± 2.5	Isidori et al (2016)
		Spain/France/Portugal	ND – 25.5 ± 2.0	Ferrando-Climent et al (2013)
		Sweden	ND	Lavén et al (2009)
		Switzerland	2.0 – 11	Buerge et al (2006)

Drug	Target analyte	Country	Concentration (ng/L)	Reference
Cyclophosphamide	Carboxycyclophosphamide	Slovenia	ND	Česen et al (2016)
			ND	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
	Ketocyclophosphamide	Slovenia	ND	Česen et al (2016)
			ND	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
	N-dechloroethyl-cyclophosphamide	Slovenia	ND	Česen et al (2016)
			ND	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
Gemcitabine	Parent	Brazil	ND - 750	de Oliveira Klein et al (2021)
		Canada	ND	Rabii et al (2014)
			ND	Vaudreuil et al (2020)
		Slovenia	ND – 61 ± 1	Isidori et al (2016)
		Spain	9.3 (Average)	Martín et al (2011)
			ND – 52.1	Martín et al (2014)
			ND	Negreira et al (2014a)
			ND	Isidori et al (2016)
Cytarabine	Parent	Canada	74.4 ± 0.9 – 924 ± 65	Vaudreuil et al (2020)
		Greece	< LOQ – 226.7	Ofrydopoulou et al (2022)
		Spain	9.2 (Average)	Martín et al (2011)
			44.4 – 464	Martín et al (2014)

Drug	Target analyte	Country	Concentration (ng/L)	Reference
Ifosfamide	Parent	Canada	ND	Vaudreuil et al (2020)
			ND	Rabii et al (2014)
		Germany	ND – 29	Kümmerer et al (1997)
		Slovenia	ND	Česen et al (2015)
			ND	Isidori et al (2016)
		Spain	3.5 (Average)	Martín et al (2011)
			ND	Ferrando-Climent et al (2014)
			ND – 19.1	Martín et al (2014)
			ND – 27.9	Negreira et al (2014a)
			ND	Isidori et al (2016)
		Spain/France/Portugal	ND – 130.1 ± 1.3	Ferrando-Climent et al (2013)
		Switzerland	ND – 5	Buerge et al (2006)
Treated wastewater				
Drug	**Type of analyte**	**Country**	**Concentration (ng/L)**	**Reference**
Capecitabine	Parent	Canada	8.62 ± 0.76 – 52.2 ± 0.6	Vaudreuil et al (2020)
		Greece	ND – < LOQ	Ofrydopoulou et al (2022)
		Japan	ND – 11	Azuma et al (2015)
		Portugal	13 – 46	Cristóvão et al (2021)
		Slovenia	ND	Isidori et al (2016)
		Spain	ND – 36.0	Negreira et al (2014a)
			ND	Isidori et al (2016)
		United Kingdom	ND	Proctor et al (2019)
Dacarbazine	Parent	Greece	ND – 84.8	Ofrydopoulou et al (2022)
Imatinib	Parent	United Kingdom	ND – 188.9	Proctor et al (2019)
			301.7 (average conc.)	Rice et al (2020)

Drug	Type of analyte	Country	Concentration (ng/L)	Reference
Fluorouracil	Parent	Brazil	ND	de Oliveira Klein et al (2021)
		Canada	ND	Vaudreuil et al (2020)
		France	ND	Mullot et al (2010)
		Slovenia	ND	Kosjek et al (2013)
			ND	Isidori et al (2016)
		Spain	ND	Martín et al (2011)
			ND	Martín et al (2014)
			< LOQ	Isidori et al (2016)
		Switzerland	ND	Tauxe-Wuersch (2005)
		USA	ND	Yu et al (2006)
			ND	Yu et al (2012)
	FBAL	Brazil	ND	de Oliveira Klein et al (2021)
Methotrexate	Parent	Canada	ND	Garcia-Ac et al (2009)
			ND – 53	Rabii et al (2014)
			ND – 25 ± 0.5	Vaudreuil et al (2020)
		Greece	3.5 – 61.0	Ofrydopoulou et al (2022)
		Italy	ND – 12.6	Castiglioni et al (2005)
		Jordan	95,000 ± 5,000 – 332,000 ± 7,000	Alahmad and Alawi (2010)
		Slovenia	ND	Isidori et al (2016)
		Spain	ND	Martín et al (2011)
			ND – 6 ± 0.1	Ferrando-Climent et al (2014)
			ND	Martín et al (2014)
			ND	Negreira et al (2014a)
			ND	Isidori et al (2016)
		Sweden	ND	Li et al (2018)
		Tunisia	ND	Afsa et al (2020)

Drug	Type of analyte	Country	Concentration (ng/L)	Reference
Methotrexate	Parent	United Kingdom	ND	Petrie et al (2016)
			ND	Proctor et al (2019)
		USA	ND	Bradley et al (2014)
	Hydroxymethotrexate	Slovenia	ND	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
Cyclophosphamide	Parent	Australia	ND	Busetti et al (2009)
			ND – 10	French et al (2015)
		Brazil	ND – < LOQ	de Oliveira Klein et al (2021)
		Canada	ND	Garcia-Ac et al (2009)
			ND – 21	Rabii et al (2014)
			ND – 18.2 ± 0.4	Vaudreuil et al (2020)
		China	ND – 110	Sun et al (2016)
		Finland	ND	Nurmi and Pellinen (2011)
		France	ND	Mullot et al (2010)
			ND	Miossec et al (2019)
		Germany	ND – 20	Ternes (1998)
		Greece	ND – 18.4	Ofrydopoulou et al (2022)
		Italy	ND – 9.0	Castiglioni et al (2005)
			ND – 791	Morosini et al (2017)
		Japan	2.8	Kadokami and Ueno (2019)
			ND – 22	Azuma et al (2015)
		Norway	ND	Thomas et al (2007)
		Poland	ND – 24.0	Kot-Wasik et al (2016)
		Portugal	ND – 17	Cristóvão et al (2021)
		Slovenia	ND – 17 ± 5	Česen et al (2015)
			17 ± 5	Isidori et al (2016)

Drug	Type of analyte	Country	Concentration (ng/L)	Reference
Cyclophosphamide	Parent	Spain	ND	Martín et al (2011)
			ND	Gómez-Canela et al (2012)
			ND	Martínez Bueno et al (2012)
			7 ± 0.3 – 25 ± 3	Ferrando-Climent et al (2014)
			ND – 5	Gómez-Canela et al (2014)
			ND	Martín et al (2014)
			ND – 25	Negreira et al (2014a)
			ND	Isidori et al (2016)
			55.94 ± 6.9 – 91.25 ± 14	Santana-Viera et al (2019)
		Sweden	ND	Lavén et al (2009)
			ND	Lundström et al (2010)
		Switzerland	~2 – 10	Buerge et al (2006)
	Carboxycyclophosphamide	Slovenia	ND	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
	Ketocyclophosphamide	Slovenia	ND	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
	N-dechloroethyl-cyclophosphamide	Slovenia	ND	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
Gemcitabine	Parent	Brazil	ND – 420	de Oliveira Klein et al (2021)
		Canada	ND	Rabii et al (2014)
			ND	Vaudreuil et al (2020)
		Slovenia	ND	Isidori et al (2016)
		Spain	7.0 (Average)	Martín et al (2011)
			ND – 88.4	Martín et al (2014)
			ND	Negreira et al (2014a)
			ND	Isidori et al (2016)

Drug	Type of analyte	Country	Concentration (ng/L)	Reference
Cytarabine	Parent	Canada	54.8 ± 4.3 – 349 ± 5	Vaudreuil et al (2020)
		Greece	ND – 10.3	Ofrydopoulou et al (2022)
		Spain	14 (Average)	Martín et al (2011)
			9.9 – 190	Martín et al (2014)
Bleomycin	Parent	United Kingdom	11 – 19	Aherne et al (1990)
Ifosfamide	Parent	Canada	ND	Rabii et al (2014)
			ND	Vaudreuil et al (2020)
		Germany	ND - 43	Kümmerer et al (1997)
			ND – 2,900	Ternes (1998)
		Slovenia	ND	Česen et al (2015)
			ND	Isidori et al (2016)
		Spain	1.2 (Average)	Martín et al (2011)
			ND	Ferrando-Climent et al (2014)
			ND – 15.6	Martín et al (2014)
			ND – 15.9	Negreira et al (2014a)
			ND	Isidori et al (2016)
		Switzerland	ND - 6	Buerge et al (2006)

ND, not detected; LOQ, limit of quantification.

Table 15 International studies assessing presence of target cytotoxic drugs in hospital wastewater

Pharmaceutical	Type of analyte	Country	Concentration (ng/L)	Reference
Capecitabine	Parent	Canada	ND – 6.13 ± 0.32	Vaudreuil et al (2020)
		Spain	ND – 1,749	Olalla et al (2018)
			ND – 490	Gómez-Canela et al (2014)
			ND	Isidori et al (2016)
		Slovenia	ND – 106 ± 6	Isidori et al (2016)
		Turkey	< LOQ – 160	Yilmaz et al (2017)
Fluorouracil	Parent	Austria	20,000 – 122,000	Mahnik et al (2004)
		Brazil	ND	de Oliveira Klein et al (2021)
		Canada	ND	Vaudreuil et al (2020)
		France	ND – 4,000	Mullot et al (2009)
			ND – 900 ± 1,200	Mullot et al (2010)
		Slovenia	ND – 92	Kosjek et al (2013)
			< LOQ – 6.9 ± 1.0	Isidori et al (2016)
		Spain	ND – 2.1 ± 0.3	Isidori et al (2016)
		Switzerland	ND	Tauxe-Wuersch (2005)
			ND – 27	Kovalova et al (2009)
			<5 – 27	Weissbrodt et al (2009)
	FBAL	Brazil	ND – 18,200	de Oliveira Klein et al (2021)
Methotrexate	Parent	Canada	ND – 68.4 ± 3.5	Vaudreuil et al (2020)
		China	ND – 4,689	Yin et al (2010a)
		Jordan	178,000 ± 4,000 – 835,000 ± 6,000 (monthly averages)	Alahmad and Alawi (2010)
		Slovenia	19 ± 2 – 3,920 ± 70	Isidori et al (2016)

Pharmaceutical	Type of analyte	Country	Concentration (ng/L)	Reference
Methotrexate	Parent	Spain	ND – 19 ± 5	Ferrando-Climent et al (2014)
			ND – 19.4	Negreira et al (2014a)
			ND – 29 ± 7	Isidori et al (2016)
			ND – 4,756	Olalla et al (2018)
		Spain/France/ Portugal	ND – < LOQ	Ferrando-Climent et al (2013)
		Tunisia	ND – 66	Afsa et al (2020)
	Hydroxymethotrexate	Slovenia	ND – 490 ± 49	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
			ND – 846	Olalla et al (2018)
Cyclophosphamide	Parent	Brazil	ND – 29,100	de Oliveira Klein et al (2021)
		Canada	ND – 2.17 ± 0.08	Vaudreuil et al (2020)
		China	ND – 2,000	Yin et al (2010a)
		France	ND – 800 ± 600	Mullot et al (2010)
		Germany	146	Steger-Hartmann et al (1996)
		Norway	ND – 21	Thomas et al (2007)
		Saudi Arabia	ND	Al Qarni et al (2016)
		Slovenia	ND – 22,000 ± 760	Česen et al (2015)
			76 – 2,686	Česen et al (2016)
			1,080 ± 200 – 22,100 ± 800	Isidori et al (2016)
		Spain	LOD – 5,730 (max conc.)	Gómez-Canela et al (2012)
			< LOQ – 43 ± 4	Ferrando-Climent et al (2014)
			ND – 4,720	Gómez-Canela et al (2014)
			ND – 100	Negreira et al (2014a)
			ND – 32 ± 1	Isidori et al (2016)
			46 – 3,000	Olalla et al (2018)
			1218 ± 45	Santana-Viera et al (2019)

Pharmaceutical	Type of analyte	Country	Concentration (ng/L)	Reference
Cyclophosphamide	Parent	Spain/France/ Portugal	<LOQ – 200.7 ± 0.9	Ferrando-Climent et al (2013)
		Switzerland	ND – 161 ± 26	Kovalova et al (2012)
		Turkey	ND - 680	Yilmaz et al (2017)
	Carboxycyclophosphamide	Slovenia	213 – 13,202	Česen et al (2016)
			17,700 ± 400 – 60,600 ± 1,000	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
	Ketocyclophosphamide	Slovenia	ND – 178	Česen et al (2016)
			270 ± 4 – 1,340 ± 10	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
	N-dechloroethyl-cyclophosphamide	Slovenia	60 – 2,099	Česen et al (2016)
			847 ± 58 – 5,520 ± 110	Isidori et al (2016)
		Spain	ND	Isidori et al (2016)
Gemcitabine	Parent	Brazil	ND – 25,900	de Oliveira Klein et al (2021)
		Canada	ND – 31.4 ± 0.1	Vaudreuil et al (2020)
		Slovenia	ND	Isidori et al (2016)
		Spain	ND	Negreira et al (2014a)
			ND	Isidori et al (2016)
			ND	Olalla et al (2018)
		Switzerland	< LOQ – 38	Kovalova et al (2009)
Cytarabine	Parent	Canada	ND	Vaudreuil et al (2020)

Pharmaceutical	Type of analyte	Country	Concentration (ng/L)	Reference
Ifosfamide	Parent	Canada	ND – 144 ± 9	Vaudreuil et al (2020)
		China	ND – 10,647	Yin et al (2010a)
		Germany	24	Steger-Hartmann et al (1996)
			ND – 1,914	Kümmerer et al (1997)
		Slovenia	ND – 6,800 ± 0.6	Česen et al (2015)
			ND – 48 ± 10	Isidori et al (2016)
		Spain	ND	Ferrando-Climent et al (2014)
			ND – 86,200	Gómez-Canela et al (2014)
			ND – 19.4	Negreira et al (2014a)
			ND	Isidori et al (2016)
			ND – 4,761	Olalla et al (2018)
		Spain/France/Portugal	ND – 227.9 ± 1.3	Ferrando-Climent et al (2013)

ND, not detected; LOQ, limit of quantification.

Table 16 International studies assessing presence of target cytotoxic drugs in drinking water

Drinking water				
Pharmaceutical	**Type of analyte**	**Country**	**Maximum concentration (ng/L)**	**Reference**
Methotrexate	Parent	France (Evian and Volvic bottled natural mineral water)	ND	Dévier et al (2013)
		USA	ND	Stackelberg et al (2004)
Cyclophosphamide	Parent	Canada	1,233	Husk et al (2019)
		China	3.72	Gu et al (2019)
		France (Evian and Volvic bottled natural mineral water)	ND	Dévier et al (2013)
		Italy	ND	Zuccato et al (2000)
		Netherlands	0.5	Houtman et al (2014)
		Poland	ND	Kot-Wasik et al (2016)
Gemcitabine	Parent	France (Evian and Volvic bottled natural mineral water)	ND	Dévier et al (2013)
Bleomycin	Parent	United Kingdom	13	Aherne et al (1990)
Ifosfamide	Parent	France (Evian and Volvic bottled natural mineral water)	ND	Dévier et al (2013)

ND, not detected.

Table 17 International studies assessing presence of target cytotoxic drugs in surface water and groundwater

River/stream				
Pharmaceutical	**Type of analyte**	**Country**	**Concentration (ng/L)**	**Reference**
Capecitabine	Parent	Japan	ND – 20	Azuma et al (2015)
		Moldova	< LOQ	Moldovan et al (2018)
		Portugal	ND	Santos et al (2018)
		Spain	ND	Franquet-Griell et al (2017a)
		United Kingdom	ND	Proctor et al (2019)
	2,3-di-O-acetyl-5-deoxy-5-fluorocytidine	Moldova	< LOQ	Moldovan et al (2018)
Imatinib	Parent	Portugal	ND	Santos et al (2018)
		United Kingdom	ND – 38.4 ± 1.3	Proctor et al (2019)
			183.3 (Average)	Rice et al (2020)
Fluorouracil	Parent	Portugal	ND	Santos et al (2018)
		Slovenia	ND	Kosjek et al (2013)
		Spain	ND	Martín et al (2011)
Methotrexate	Parent	Canada	ND	Garcia-Ac et al (2009)
		Spain	ND	Martín et al (2011)
			ND – 5 ± 0.2	Ferrando-Climent et al (2014)
		United Kingdom	ND	Proctor et al (2019)
		USA	ND	Bradley et al (2014)
			ND – 161	Elliott et al (2017)
			ND – 34	Bradley et al (2019)

Pharmaceutical	Type of analyte	Country	Concentration (ng/L)	Reference
Cyclophosphamide	Parent	Belgium	ND	Chauveheid and Scholdis (2019)
		Canada	ND	Garcia-Ac et al (2009)
		Germany	ND	Ternes (1998)
		Italy	ND – 10.1	Zuccato et al (2000)
		Japan	ND – 20	Azuma et al (2015)
			ND – 4.8 (Average)	Hanamoto et al (2014)
			ND – 9.2	Tamura et al (2017)
		Moldova	< LOQ	Moldovan et al (2018)
		Netherlands	ND – 0.5	Houtman et al (2013)
		Poland	ND – 3.6	Kot-Wasik et al (2016)
			0.09 – 0.94	Czernych et al (2014)
		Portugal	ND	Santos et al (2018)
		Romania	< LOQ – 64.8 ± 8.0	Moldovan (2006)
		Spain	ND – 20 ± 4	Ferrando-Climent et al (2014)
			ND	Martín et al (2011)
			ND – 13.7	Franquet-Griell et al (2017a)
		Switzerland	~ 0.05 – 0.17	Buerge et al (2006)
		Vietnam	ND – 0.92	Ngo et al (2021)
Gemcitabine	Parent	Moldova	< LOQ	Moldovan et al (2018)
		Spain	2.4 (Average)	Martín et al (2011)
	2',2'-Difluoro-2'-deoxyuridine	Moldova	ND	Moldovan et al (2018)
Cytarabine	Parent	Moldova	< LOQ	Moldovan et al (2018)
		Spain	13 (Average)	Martín et al (2011)
Bleomycin	Parent	United Kingdom	ND – 17	Aherne et al (1990)

Pharmaceutical	Type of analyte	Country	Concentration (ng/L)	Reference
Ifosfamide	Parent	Germany	ND	Ternes (1998)
		Spain	ND	Martín et al (2011)
			ND	Ferrando-Climent et al (2014)
			10.1 – 13.9	Franquet-Griell et al (2017a)
			ND – 41	Valcárcel et al (2011)
		Switzerland	ND – ~ 0.14	Buerge et al (2006)
Lake				
Pharmaceutical	**Type of analyte**	**Country**	**Concentration (ng/L)**	**Reference**
Cyclophosphamide	Parent	Canada	5 (max)	Hull et al (2015)
		Poland	ND – 5.0	Czernych et al (2014)
		Switzerland	~ 0.07	Buerge et al (2006)
Groundwater				
Pharmaceutical	**Type of analyte**	**Country**	**Concentration (ng/L)**	**Reference**
Methotrexate	Parent	USA	ND – 14	Bradley et al (2014)
Cyclophosphamide	Parent	New Zealand	ND – 6.4	Moreau et al (2019)
Unspecific				
Pharmaceutical	**Type of analyte**	**Country**	**Concentration (ng/L)**	**Reference**
Methotrexate	Parent	Tunisia (Coastal water)	ND	Afsa et al (2020)
Cyclophosphamide	Parent	Australia (harbour)	ND	French et al (2015)
		Canada (urban wetland)	ND – 6.15	Muir et al (2017)

ND, not detected; LOQ, limit of quantification.

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