

Chemotherapeutic drugs in Lebanese surface waters: estimation of population exposure and identification of high-risk drugs

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Abstract

Environmental risk assessment of anti-cancer drugs and their transformation products is a major concern worldwide due to two main factors: the consumption of chemotherapeutic agents is increasing throughout the years and conventional water treatment processes seem to be ineffective. The aim of the study is to investigate the consumption of anticancer drugs and assess their potential health hazard as contaminants of the Lebanese surface waters. Data on yearly consumption of 259 anti-neoplastic drugs over the years 2013 to 2018 were collected and the following parameters were calculated: yearly consumption of single active ingredients, yearly consumption of drug equivalents (for drugs belonging to the same pharmacologic class/ having the same active ingredient) and Predicted Environmental Concentrations (PECs). The classification of compounds into risk categories was based on exposure using PECs. The top five most commonly consumed drugs are Mycophenolate mofetil, Hydroxycarbamide, Capecitabine, Mycophenolic acid and Azathioprine. Based on the calculated PEC values of single active ingredients as well as their equivalents, six high risk priority compounds were identified: Mycophenolate mofetil, Hydroxycarbamide, Capecitabine, Mycophenolic acid and Azathioprine and 5-Fluorouracil. The impact of these micropollutants on animals as well as humans was analyzed. This research paper stresses the importance of further analysis of chemotherapy micropollutants with major focus on high risk drugs. Additionally, regulations should be set in place to ensure proper management of waste water and the development of efficient waste water treatment plants.

1. Introduction

Cancer is the second leading cause of death in the world. Every sixth death in the world is due to cancer [1]. In Lebanon, the number of new cancer cases diagnosed in 2018 is 17294 cases (288 cases per 100,000 population) with breast, bladder, lung, prostate, and colorectal cancers being the most common [2]. The number of death from cancer has doubled between the years 2000 (3776 deaths) and 2017 (6639 deaths) with a relative increase in less than 1.5 M in Lebanese population [2]. As the world population is growing and aging, the global number of cancer death is expected to increase further. Chemotherapy is often used as a major treatment for almost all types of cancer. Cytotoxic drugs are a group of compounds used in chemotherapy to prevent or disrupt cell division. There are over 50 cytotoxic drugs used routinely in chemotherapy.

Chemotherapeutic agents can be classified into different categories based on their chemical structures and the way they act on cancer cells. Most commonly used agents are *alkylating agents*, which act directly on DNA, causing cross-linking of DNA strands, abnormal base pairing, or DNA strand breaks, thus preventing the cell from dividing. Another class of commonly used chemotherapeutic drugs are *antimetabolites*, which replace natural substances as building blocks in DNA molecules, thereby altering the function of enzymes required for cell metabolism and protein synthesis. *Plant alkaloids* are antitumor agents derived from plants. These drugs act specifically by blocking the ability of a cancer cell to divide and become two cells. Another major class are *antitumor antibiotic*. They act by binding with DNA and preventing RNA synthesis, a key step in the creation of proteins, which are necessary for cell survival. Many of these drugs are mutagenic, carcinogenic, teratogenic and/or toxic to reproductive systems and are classified as highly hazardous compounds [3].

Anticancer drugs present as a major water contaminant worldwide; Lebanon's case is not less worrisome. Environmental risk assessment of anti-cancer drugs and their transformation products is a major concern worldwide; studies have been conducted to analyze chemotherapy drugs consumption trends, availability in

surface water and population exposure. This is due to two main factors: the consumption of chemotherapeutic agents is increasing throughout the years and conventional water treatment processes seem to be ineffective. Many research studies reported that waste water treatment plants (WWTPs), even those that meet regulatory requirements for waste water treatment, are only moderately effective in removing the aforementioned pharmaceuticals[4–7]. The pharmacologic properties and mutagenic properties of chemotherapy drugs potentially make anticancer drugs the most dangerous contaminant of our water system and pose a risk to the aquatic life and human beings. Available ecotoxicological data for anti-cancer drugs and their metabolites are incomplete. So far, the situation in Lebanon was not evaluated by any environmental risk assessment studies. Our work is the first to present an overview of the consumption trends in Lebanon, to forecast the presence of the associated contaminants in surface waters, and to conclude with an assessment of the correlated risks. The assessment will take into consideration the pharmacokinetic properties (metabolism and excretion) of each of the anticancer drugs analyzed.

The aim of the study is to investigate the consumption of anticancer drugs and assess their potential health hazard toxic effects as contaminants in the environment.

2. Materials And Methods

The work is divided into five steps:

- Study the consumption of chemotherapy drugs in Lebanon over the years 2013 to 2018.
- Compute the concentration of these drugs in surface water.
- Investigate the exposure of the Lebanese population to anticancer drugs.
- Assess the long term risks associated with this exposure and the potential effect on Lebanon as well as countries on the Mediterranean Sea.

2.1 Anticancer drugs consumption

The brand names of cancer drugs available on the Lebanese market and registered at the Ministry of Public Health (MOPH) were identified, and the yearly consumption of each drug consumed between 2013 and 2018 was studied. Data comprised all the dosage forms available on the Lebanese market including tablets, capsules and injectable drugs. As per the MOPH, anticancer drugs are classified as: endocrine therapy, immunosuppressive agents and antineoplastic agents.

2.2 Data collection and concentration in surface water

Consumption data was identified for 259 anti-neoplastic drugs over six years. The total amount of active ingredients consumed over the years was calculated based on the following:

- For every brand drug, consumption per year (in mg) was calculated using the number of boxes (preparations) consumed \times the number of units/box and the amount of active ingredients in each unit (in mg).
- Drugs with the same active ingredient were grouped together and their consumption was summed up.

- When applicable, different active ingredients belonging to the same pharmacologic or chemical class were grouped together. Total consumption in every drug class was calculated using conversion factors, as provided in Table 1.
- Cumulative concentration was calculated by summing the total consumption per year for the years 2013 to 2018.

2.3 Exposure based classification

Pharmaceuticals that are used in higher amounts have a potential to reach the aquatic environment in greater quantities and therefore present a higher risk to human and aquatic life. Therefore, risk classification is done according to quantity consumed. The classification of compounds based on exposure is done using Predicted Environmental Concentrations (PECs), according to Scheme 1. Thresholds for risk classification adopted in the analysis are 100 ng L⁻¹ (guidance by the Food and Drug Administration- FDA [14] and 10 ng L⁻¹ (guidance by European Medicine Agency- EMEA [15] Two PEC values were determined:

- PEC_a assumes no metabolism of the active ingredient happens in the body, 100% of the active ingredient is excreted unchanged.

$$(1) \text{ PEC}_a = \frac{\text{consumption}}{W \text{Winhab} \times \text{inhab} \times \text{DF}}$$

Where Consumption is the amount of active ingredient consumed per year (ng year⁻¹) WWinhab is the water consumption per person per year, Inhab is the number of inhabitants of Lebanon and DF is the dilution factor from WWTPs effluents to surface water.

- PEC_b is calculated when metabolism data is available for the drug. The fraction of active ingredient excreted unchanged (F_{exc}) is added to the equation.

$$(2) \text{ PEC}_b = \frac{\text{consumption}}{W \text{Winhab} \times \text{inhab} \times \text{DF}} \times F_{exc}$$

- PEC_c is the predicted concentration in surface water that remains after treatment. Therefore, PEC_c is obtained by taking into consideration the fraction of pharmaceuticals removed by WWTPs (F_{WWTP}). However, due to the absence of efficient treatment plants or the absence of data in Lebanon, the F_{WWTP} was assumed to be equal to zero. PEC_c and PEC_b values are therefore equal.

$$(3) \text{ PEC}_c = \frac{\text{consumption}}{W \text{Winhab} \times \text{inhab} \times \text{DF}} \times F_{exc} \times (1 - F_{\text{WWTP}})$$

The following assumptions were made when using the formula:

- According to the EMEA guidelines, the amount of waste water per inhabitant per day to be equal to 200 L. The yearly consumption (WW_{inhab}) would therefore be equal to $7300 \text{ L inhab}^{-1} \text{ year}^{-1}$ [15].
- The number of inhabitants in Lebanon was assumed to be equal to 6,000,000 [16].
- The Dilution Factor was assumed to be equal to 10 as per the EMEA guidelines.
- The fraction of active ingredient excreted unchanged was assumed to be equal to 0.5 when data was not available.

2.4 Toxicity classification

Depending on PEC_a and PEC_b values obtained for each drug, a different class was assigned to each drug. Drugs were categorized into six classes from the highest to the lowest risk, as explained in table 2.

3. Results

3.1 Anticancer drugs consumption in Lebanon

The top five drugs with the highest total consumption (2013- 2018) are the following (in decreasing order): Mycophenolate mofetil (MMF), Hydroxycarbamide, Capecitabine, Mycophenolic acid (MPA) and Azathioprine (figure 1).

The most consumed drug, MMF, is an ester prodrug of MPA, classified as a reversible inhibitor of inosine monophosphate dehydrogenase. Once orally administered, MMF is rapidly converted into its active form MPA by hepatic carboxylesterases 1 and 2 [18,19]. Therefore, MMF should be considered as a source of MPA in terms of environmental contamination. Accordingly, consumption data of both drugs were grouped together based on the conversion factor presented in table 1. The yearly consumption of both drugs and their equivalent total MPA is presented in figure 2.

The second most commonly consumed drug is Hydroxycarbamide, also known as hydroxyurea. Hydroxycarbamide is an antineoplastic agent that inhibits DNA synthesis through the inhibition of ribonucleoside diphosphate reductase. Once administered, Hydroxyurea is converted to a free radical nitroxide in vivo [20]. The third most commonly consumed drug is capecitabine, an orally-administered chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers. Capecitabine is a prodrug that is enzymatically converted to fluorouracil (antimetabolite) in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissue [9,21]. The environmental toxicity of capecitabine should therefore be analyzed as part of that of Fluorouracil. The yearly consumption of both drugs and their equivalent 5-Fluorouracil is presented in figure 3. The fourth most commonly consumed drug is MPA and the fifth is azathioprine, a purine analogue with cytotoxic and immunosuppressive activity. It is prodrug of 6-mercaptopurine [22]. Figure 4 illustrates the change in the consumption of each of the commonly consumed chemotherapeutic drugs over the years 2013-2018.

3.2 Exposure-based classification

In the first section, the results illustrate the amount of anticancer drugs consumed in Lebanon. In this section, however, in order to better reflect on the exposure to anticancer drugs, several factors are considered (excretion

and WWTPs removal rates). First, the concentration of each anticancer drug in surface waters was predicted without regard to transformation in the body and removal at WWTPs. This value (PEC_a) is an illustration of the worst case scenario. Then, a new PEC value - PEC_b - was determined with consideration of the drugs' biotransformation in the body. A third PEC value, PEC_c , should ideally be calculated to take into consideration the fraction of the drug removed by WWTP. However, due to the absence of efficient WWTP in Lebanon and the absence of data, the PEC_c value calculated would be equal to PEC_b . Details on the PEC_a and PEC_b results along with the classification of the drugs are presented in a separate document. As we can see in table 3, most of the drugs belong to class IV and class III, both indicative of a very low risk of environmental toxicity. High risk compounds (class IA) include MMF and MMF equivalent. Potentially hazardous compounds, belonging to class II, include azathioprine, capecitabine, Hydroxycarbamide and MPA, and 5-fluorouracil equivalent. Therefore, from the 259 anti-neoplastic agents available on the Lebanese market, the previously enumerated 6 compounds should be considered as priority for further evaluation. Figure 5 presents the PEC_b value for the priority anticancer drugs.

4. Discussion

4.1 Analysis of the results

MMF is the most commonly consumed drug. The main reason behind the elevated consumption of MMF prodrug and its active ingredient MPA is that they are used for as both chemotherapeutic and immunosuppressive agents in organ transplantation as well as auto-immune disease [19]. The analysis of the toxicity of MMF and MPA each separately led to an underestimation of the risks imposed by this drug. Since MMF is a prodrug of MPA, the consumption of both was grouped using drug-specific equivalence factors under a total MPA equivalent (table 1). The PEC values calculated for the MPA equivalent led to risk categorization of the MPA equivalent into either class IIA or class IA for different years, indicating that MPA is a potentially hazardous compound. In contrast, when MPA was analyzed as a separate entity of MMF, it was classified into class IIA and class III for different years, underestimating its potential toxicity. The consumption trend of MMF and MPA was consistent between the years 2013 and 2018. In comparison with global consumption, MMF consumption in Lebanon is $329.22 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$, lower than its consumption in Portugal ($593 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [17]. As for MPA, its consumption in Lebanon equals $72.03287 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$, higher than in Portugal ($50 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [17] and Poland ($51 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [23] but lower than in Catalonia ($704 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [24].

The second most commonly consumed drug is hydroxycarbamide. This could be explained by the fact that hydroxycarbamide is highly consumed in the Middle East and Africa region and it is relatively cheaper than other chemotherapeutic drugs and has several indications [25]. Its consumption approximately doubled between the years 2013 and 2018. It was classified, according to the calculated PEC values, in class IIA (potentially hazardous compounds) for the years 2013-2018. In comparison with global consumption, the consumption of hydroxycarbamide in Lebanon is equal to $140.97 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$, higher than in the UK ($33 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [26] but lower than in Portugal ($253 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [17], Catalonia ($221 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [24] and France ($284 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [27].

The third most commonly consumed drug is Capecitabine. Capecitabine is a widely used chemotherapeutic drug as it has gained approval in two of the most common cancers in Lebanon: breast and colorectal cancer [2]. Additionally, There is a global trend towards the prescribing of capecitabine over fluorouracil as capecitabine allows more patient-friendly oral administration, improved quality of life and fewer side effects [28]. It is worth noting that consumption data of fluorouracil for the years 2014 to 2016 was absent from the provided data. Accordingly, we could not have a clear image on the extent/trend in its consumption. As previously mentioned in the results section, capecitabine is a prodrug of 5-fluorouracil. Accordingly, the consumption of both was grouped using drug-specific equivalence factors under a total 5-fluorouracil equivalent. The PEC values calculated for the equivalent lead to its risk categorization into class IIA for the years 2013-2018, indicating that 5-fluorouracil is a potentially hazardous compound. This again proves that a separate analysis of capecitabine and 5-fluorouracil will lead to an underestimation of the toxicity of each of the drugs, as 5-fluorouracil analyzed separately was classified into class IV (very low risk). The consumption of capecitabine decreased by one-third between the years 2013 and 2018. In comparison with global consumption, the consumption of capecitabine in Lebanon is equal to $133.09 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$, lower than its consumption in Portugal ($206 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [17], Catalonia ($280 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [24], France ($213 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [27], and UK ($183 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [26]. As for 5-fluorouracil, its consumption in Lebanon is equal to $6.69 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$ and it is higher than its consumption in Catalonia ($0.70 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [24] and lower than Portugal ($62.50 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [17], France ($71. \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [27] and UK ($46 \mu\text{g Inhabitant}^{-1} \text{Day}^{-1}$) [26].

The fifth most commonly consumed drug is Azathioprine. Azathioprine labeled indications are kidney transplantation and rheumatoid arthritis. Its use can be explained by the wide prevalence of rheumatoid arthritis disease in the Lebanese population versus the global population, 1% and 0.5 to 1%, respectively [29]. Its consumption has remained the same between years 2013 and 2018. Azathioprine was classified, according to the calculated PEC values, in class IIA (potentially hazardous compounds) for the years 2013-2018.

4.2 Actual Risk

In this study, we have analyzed the risk imposed by chemotherapeutic micro-pollutants based on their yearly consumption. However, in fact, some chemotherapeutic drugs accumulate and their amounts in the environment build up over the years, alluding to a higher ecotoxicological risk. A review of the environmental fate of the top 5 most consumed drugs reveals that none of them is a potential bio-accumulative drug [9,28,30]. However, less commonly consumed chemotherapy drugs that can accumulate and potentially pose a serious environmental risk include: Cyclophosphamide, Ifosfamide [31] and Erlotinib [32].

Another factor that should be taken into consideration is that the residues of pharmaceuticals occur in the environment as complex mixtures, and therefore, even though the concentrations of an individual compound might be low, the cocktail effect might have a more concerning ecotoxicological implication. Research studies on the environmental concern of combinations of anticancer drugs revealed that the interactions of anticancer drugs could be of environmental concern [33–35].

4.3 Impact on animals/humans

Studies investigating the toxicity of chemotherapy drugs on animals are scarce and are usually done using higher concentrations than those found in the environment. Accordingly, additional work is needed to evaluate the acute and chronic risks associated with exposure to environmental concentrations. MPA risk evaluation studies revealed that it can cause growth inhibition in green algae. The germination as well as root growth of certain seeds was significantly inhibited by MPA in a concentration-dependent manner. Additionally, the exposure of the cyano-bacterium *A. flos-aquae* to MPA resulted in a clear concentration–response relationship on the growth rate of the bacteria [36]. A study by Kovacs et al. (2015) evaluated the chronic exposure of zebrafish to 5-Fluorouracil at environmentally relevant concentrations. The results revealed that such exposure causes hepatic and renal histopathological changes, DNA damage and massive whole-transcriptome changes [37]. Another study by Mišić et al. (2016) reports an increased frequency of abortive grains in higher plants exposed to 5-fluorouracil [38].

In addition, with the geographical location of Lebanon in mind, we cannot but highlight the impact of those micropollutants on neighboring countries that share the Mediterranean Sea, including but not limited to Algeria, Croatia, Cyprus, Egypt, France and Greece.

4.4 The need for regulations

4.4.1 The importance of WWTPs

Pharmaceutical compounds are designed to have desirable target effects in the human body, but the impact of chronic indirect exposure to these compounds can be dangerous for both humans as well as other species. Anticancer drugs have potent cytotoxic, genotoxic, mutagenic, carcinogenic, endocrine disruptor as well as teratogenic effects. The augmentation of cancer disease in the Lebanese population has led to an increase in the drug consumption and therefore an increase in drug discharge into the environment. Therefore, it is indeed essential to pay special attention to the discharge of anticancer drugs in the environment and the development of effective WWTPs. It is worth noting that not all waste water treatment techniques are effective at removing anticancer drugs. The scarce literature available shows that a promising method for the removal of micropollutants is the membrane bioreactor (MBR), which combines physical removal with biological removal (biodegradation) to improve the outcome of the water treatment [6].

4.4.2 Pharmaceutical waste management in Lebanon

In this paper, we have tackled the risks imposed by a major source of chemotherapeutic drug in surface waters: the chemotherapeutic drugs consumed by the patients in medical centers as well as their home. However, another major source of micropollutants are expired/unused drugs that stay at the importer's warehouses and do not reach hospitals/patients. In the absence of a safe solution and the necessary regulations to dispose of pharmaceutical surplus, warehouses in Lebanon are filling up with old, expired drugs [39].

4.4.3 Need for regulations

Efforts are needed to set new policies regarding the disposal of micropollutants in general, and chemotherapeutic drugs primarily. We hope that this research study sheds light on the risk imposed by chemotherapeutic drugs and contributes to future establishment and enforcement of regulations to protect the public from the danger of such micropollutants in surface waters.

4.5 Future studies needed

Our research study is the first of its kind in Lebanon and the Middle East. As previously stated, in this study, we have estimated the environmental concentrations in surface waters by the calculation of PECs based on consumption data. Reports on the occurrence of chemotherapeutic drugs in surface water, ground water or drinking water by measurement of actual of the drug concentrations are absent.

5. Conclusions

This work presents, for the first time, an extensive analysis of the consumption rates of 259 different anticancer drugs dispensed in Lebanon between 2013 and 2018. Globally, there is a growing attention regarding the fate of pharmaceuticals in the environment and their potential toxicity to different species. All pharmaceuticals, by design, are meant to elicit a biological response. Chemotherapeutic drugs are of a particular concern, as these drugs were designed to damage DNA, inhibit DNA synthesis, and interrupt cell replication. They act unselectively on all growing cells and have mutagenic potency. The analysis showed that the top five most commonly consumed drugs are: MMF, hydroxycarbamide, capecitabine, MPA and azathioprine. A preliminary analysis of the toxicity risk based on the assessment of exposure allowed the identification of six potentially priority drugs, belonging to classes IA (high risk compounds) and IIA (potentially hazardous compounds): MMF, hydroxycarbamide, capecitabine, MPA, azathioprine and 5-fluorouracil. Our analysis has also proven that, when analyzing the potential risk of such micropollutants, it is a key pre-requisite to combine drugs with common end product, as their toxicity cannot be separated. Further analysis of these priority micropollutants is necessary, with actual measurement, rather than estimation, of their occurrence in surface waters. In this study, we have shed light on potential contaminants of our surface waters, emphasizing the importance of efficacious WWTPs and the enforcement of regulations with regard to environmental pollution.

Declarations

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Availability of data and materials:

All data generated or analyzed during this study are included within the article except for the raw data provided by the MOPH, which will be provided upon request.

Authors' contributions:

Y. Saab was responsible for the conceptualization and design of the study, acquisition of the data and critical data analysis and revision of the manuscript. Z. Nakad developed the software needed for the calculations and processed the data. R. Rahme worked on the computation and interpretation of data and drafted the article. All authors read and approved the final manuscript.

Competing interests:

The authors declare they have no competing interests.

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Tables

Table 1 Active ingredients in each class of anticancer drugs and the factors used in the conversion.

Drug class	Active ingredients	Conversion factor
Inosine monophosphate dehydrogenase inhibitor	<ol style="list-style-type: none"> 1. Mycophenolic acid (MPA) 2. Mycophenolate mofetil (MMF) 	1440 mg MPA = 2000 mg MMF [8]
Antimetabolites	<ol style="list-style-type: none"> 1. Capecitabine 2. 5-Fluorouracil 	2.76 mg CAP = 1 mg 5-Fluorouracil [9]
Alkylating agents	<ol style="list-style-type: none"> 1. Cyclophosphamide 2. Ifosfamide 	1 mg cyclophosphamide = 0.244 ifosfamide [10]
Anthracyclins	<ol style="list-style-type: none"> 1. Epirubicin HCl 2. Mitoxantrone 3. Doxorubicin 4. Idarubicin HCl 	75 mg Epirubicin = 12.5 mg Mitoxantrone = 50 mg Doxorubicin = 10mg idarubicin [11]
Taxanes	<ol style="list-style-type: none"> 1. Docetaxel 2. Paclitaxel 	135 mg Paclitaxel = 75 mg Docetaxel
Antimetabolites	<ol style="list-style-type: none"> 1. Methotrexate 2. Pemetrexed 	1.5 mg Methotrexate = 150 mg Pemetrexed [12]
LHRH agonist: equivalent	<ol style="list-style-type: none"> 1. Goserelin 2. Leuprorelin 3. Triptorelin 	3.6 mg Goserelin = 7.5 mg Leuprorelin = 3.75 mg Triptorelin [13]

Table 2 Classification of compounds based on potential exposure (PEC_a and PEC_b values): risk categories.

Class	Risk
Class IA	High risk compounds
Class IB	Potentially hazardous compounds but limited data
Class IIA	Potentially hazardous compounds
Class IIB	Unclassified risk
Class III	Very low risk
Class IV	Very low risk

Table 3 Risk categorization of chemotherapeutic drugs based on environmental exposure data between 2013 and 2018.

CLASS IA	Class IIA	Class III	CLASS IV		
Mycophenolate mofetil (2013-2016)	Azathioprine (2013-2015,2017-2018)	Mycophenolic acid (2013)	Imatinib (2017-2018)	Epirubicin HCl	Pomalidomide
Mycophenolic acid equivalent (2016)	Capecitabine	Tamoxifen (2015-2018)	Afatinib	Eribulin mesylate	Regorafenib
	Hydroxycarbamide	Imatinib (2013-2016)	Imatinib	Erlotinib	Ribociclib
	Mycophenolate mofetil (2015, 2017,2018)	Azathioprine (2016)	Alectinib	Etoposide	Ruxolitinib
	Mycophenolic acid (2014-2018)	Ciclosporin (2014)	Anastrozole	Everolimus	Sirolimus
	Mycophenolic acid equivalent (2013-2015, 2017-2018)		Apremilast	Exemestane	Sorafenib
	5-fluorouracil equivalent		Axitinib	Fingolimod	Sunitinib maleate
			Azacitidine	Fludarabine	Tacrolimus monohydrate
			Baricitinib	Fluorouracil	Temozolomide
			Bendamustine HCl	Fulvestrant	Teriflunomide
			Bicalutamide	Gefitinib	Thalidomide
			Bleomycin	Goserelin	Tofacitinib
			Busulfan	Ibrutinib	Trabectedin
			Cabazitaxel	Idarubicin HCl	Trifluridine
			Carboplatin	Ifosfamide	Triptorelin
			Carfilzomib	Irinotecan HCl	Vemurafenib
			Ciclosporin (2013,2015-2018)	Lapatinib ditosylat	Venetoclax
			Cisplatin	Leflunomide	Vincristine sulfate
			Clofarabine	Lenalidomide	Vinorelbine
			Cladribine	Lenvatinib	Vismodegib
			Crizotinib	Letrozole	Oxaliplatin
			Cyclophosphamide	Leuprorelin	Gemcitabine
			Cytarabine	Mercaptopurine	Methotrexate
			Dacarbazine	Mitoxantrone	Tamoxifen (2013-2014)
			Dasatinib	Nilotinib	
			Decitabine	Nintedanib	
			Degarelix	Osimertinib	
			Docetaxel	Paclitaxel	

Doxorubicin	Palbociclib	Methotrexate
Enzalutamide	Pazopanib HCl	equivalent
	Pemetrexed	Docetaxel
	Plerixafor	equivalent
	Methotrexate	Doxorubicin
	equivalent	equivalent
		Goserelin
		equivalent

Table 4 PECa, PECb and risk categorization of the priority anticancer drug and their corresponding equivalents between the years 2013 and 2018.

Active Ingredient	factor	2013	2014	2015	2016	2017	2018
Azathioprine	PECa	46.94	29.61	27.37	13.08	26.97	51.14
	PECb	23.47	14.8	13.68	6.54	13.48	25.57
	Class	IIA	IIA	IIA	III	IIA	IIA
Capecitabine	PECa	98.98	74.17	83.78	83.17	83.17	54.38
	PECb	49.49	37.08	41.89	41.58	41.58	27.19
	Class	IIA	IIA	IIA	IIA	IIA	IIA
5- fluorouracil	PECa	1.49	NA	NA	NA	1.92	7.95
	PECb	0.74	NA	NA	NA	0.96	3.97
	Class	IV	NA	NA	NA	IV	IV
Mycophenolic acid	PECa	12.19	41.31	62.09	56.65	38.43	43.41
	PECb	6.10	20.66	31.05	28.33	19.21	21.70
	Class	III	IIA	IIA	IIA	IIA	IIA
Mycophenolate mofetil	PECa	218.05	212.46	167.76	233.49	161.20	185.93
	PECb	109.03	106.23	83.88	116.74	80.60	92.97
	Class	IA	IA	IIA	IA	IIA	IIA
Hydroxycarbamide	PECa	64.77	117.93	73.10	54.83	77.10	115.25
	PECb	32.38	58.96	36.55	27.41	38.55	57.62
	Class	IIA	IIA	IIA	IIA	IIA	IIA
Mycophenolic acid equivalent	PECa	169.19	194.28	182.88	224.76	154.49	177.28
	PECb	84.59	97.14	91.44	112.38	77.25	88.64
	Class	IIA	IIA	IIA	IA	IIA	IIA
5-fluorouracil equivalent	PECa	37.35	26.87	30.36	30.14	32.06	27.65

PECb	18.67	13.44	15.18	15.07	16.03	13.83
Class	IIA	IIA	IIA	IIA	IIA	IIA

Figures

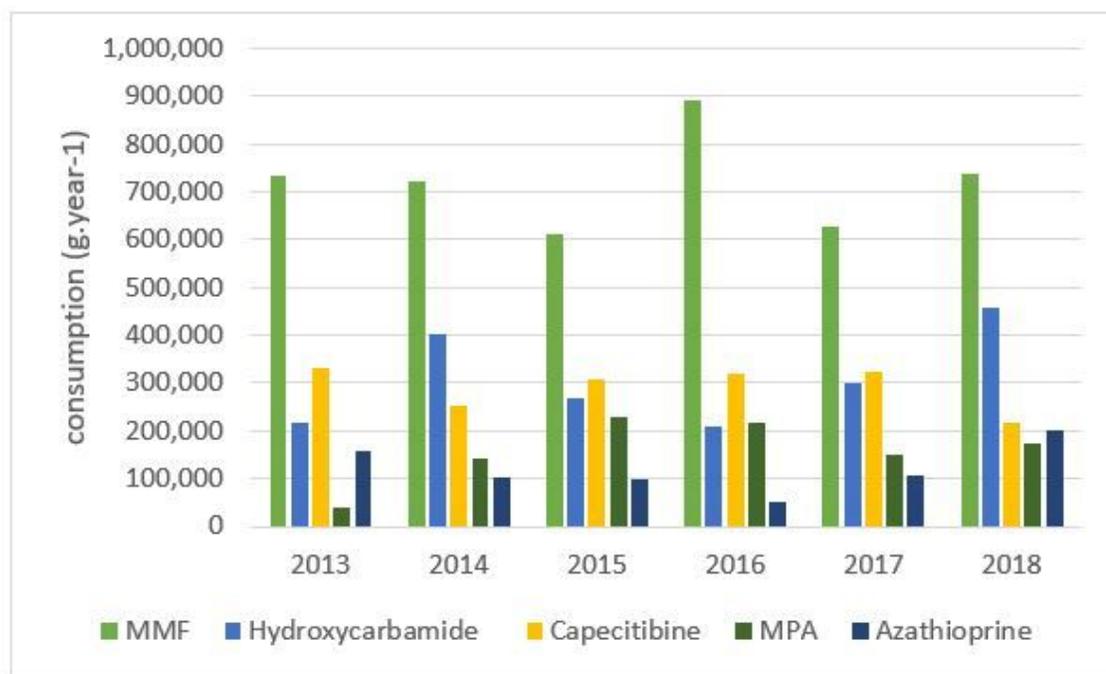


Figure 1

Top 5 most commonly consumed anticancer drugs in Lebanon between 2013 and 2018.

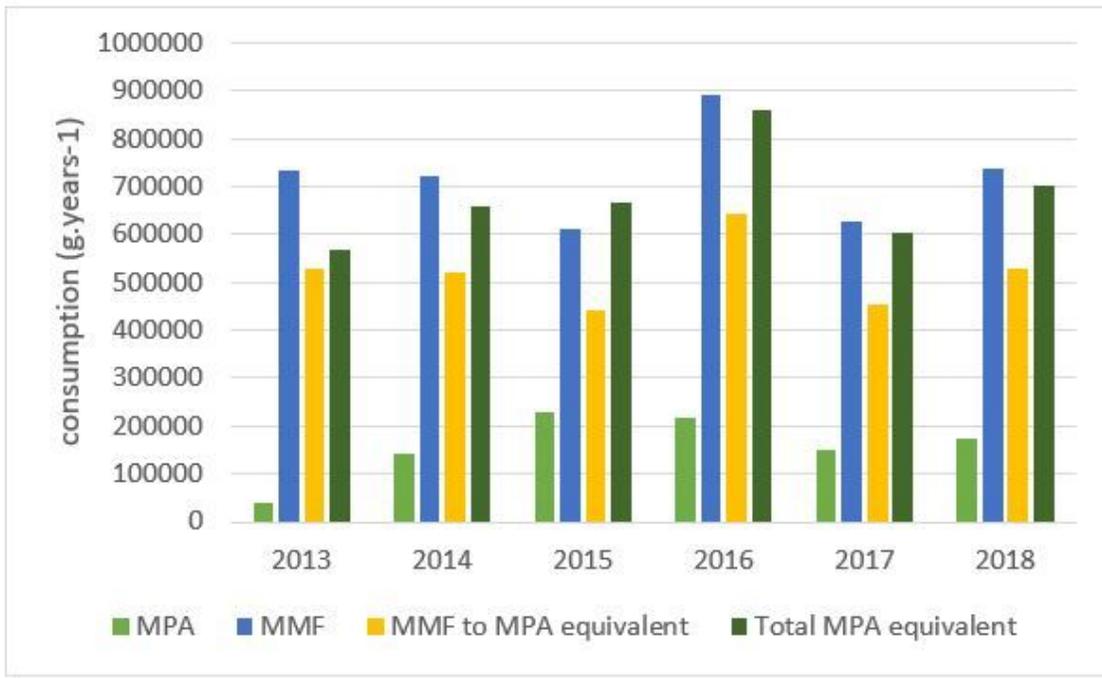


Figure 2

Yearly consumption of MMF, MPA and their equivalent MPA between 2013 and 2018.

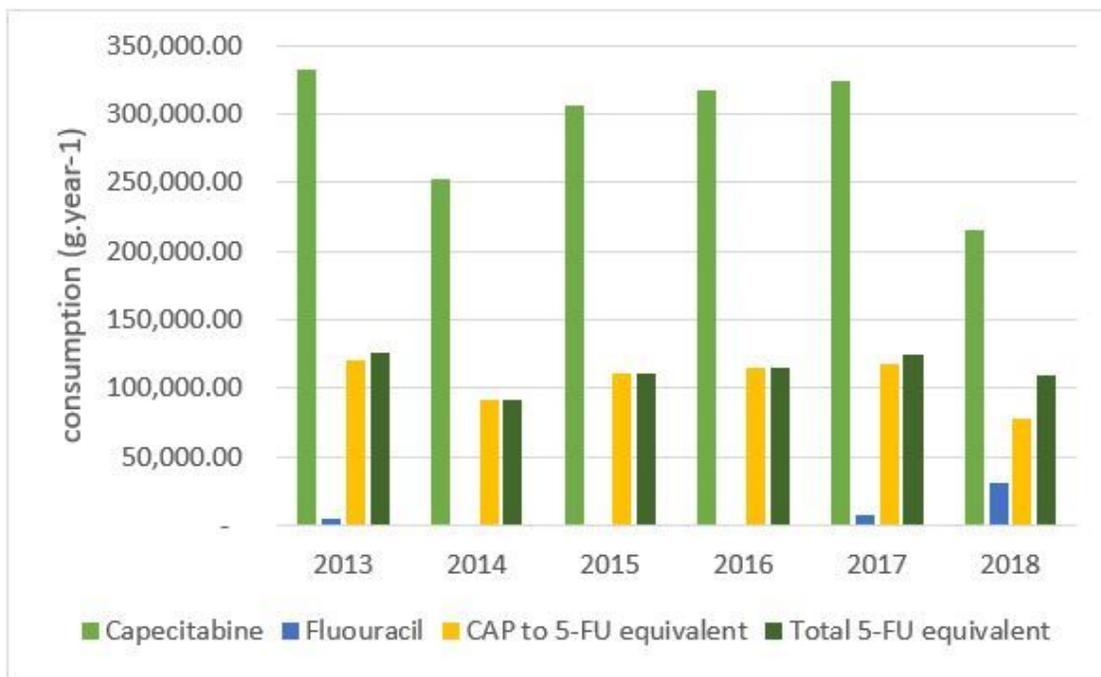


Figure 3

Yearly consumption of capecitabine, 5-fluorouracil, and their equivalent (2013-2018).

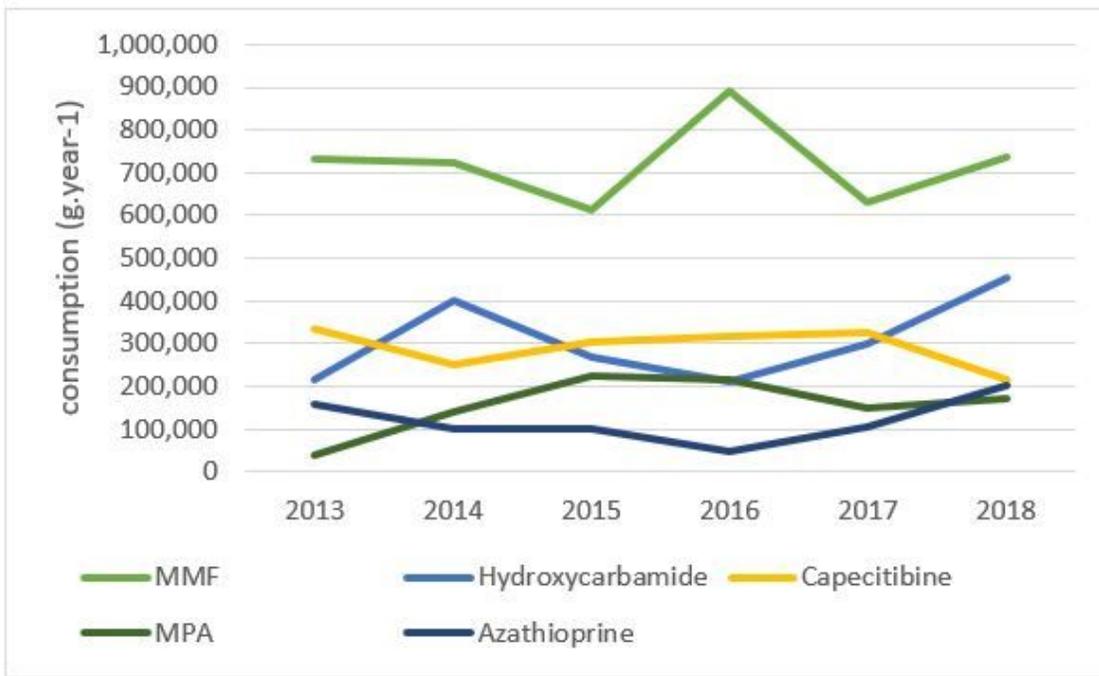


Figure 4

Trend in the consumption of commonly prescribed chemotherapeutic drugs (2013-2018).

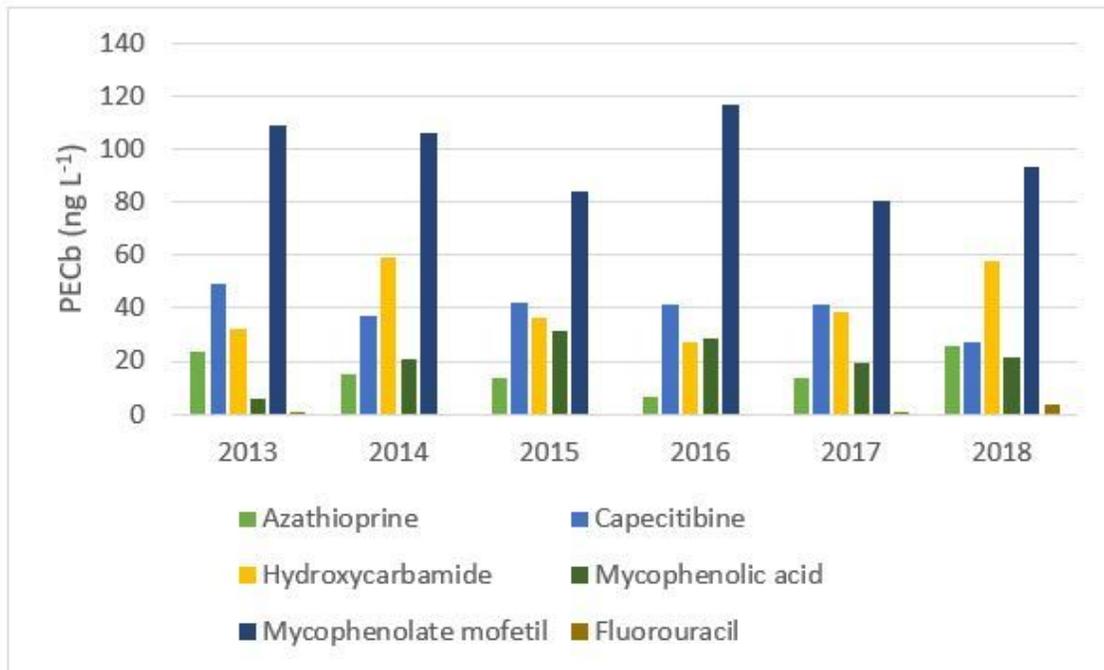


Figure 5

PEC b value of the 6 priority chemotherapeutic drugs in Lebanon.

Supplementary Files

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- [Scheme1.jpg](#)