Cytotoxic Drug Contamination in Hospital and Municipal Wastewater and Its Transfer to Surface Water

Pharma-Cycle Inc.
Theresa L. O'Keefe, Ph.D.
Chief Scientific Officer

September 21, 2011

Introduction

DNA mutating cytotoxic chemotherapy drugs are highly effective against many types of cancer and critical for saving lives. Unfortunately, a number also pass through the patient and into the wastewater system. Recent research has discovered that these drugs can survive wastewater treatment systems and are being found in surface water, the source of drinking water. This is a major concern because drinking water with low levels of cytotoxic drugs could cause damage to the most vulnerable members of our society – the unborn, babies and children.

Cytotoxic Chemotherapy Drugs and Their Method of Action

Chemotherapy drugs are potent, life-saving treatments for patients with many types of cancer. Their methods of action involve interrupting the cellular functions of fast growing cells and when possible trigger cell death. In a cancer patient, fast growing cells tend to be cancer cells so these are the cell type most affected by these drugs. However other fast growing cells (e.g. hair) are also affected. The biologic pathways targeted by a major subgroup of cytotoxic chemotherapies include DNA replication and repair functions. This subgroup's drugs are designated as Genotoxic drugs and cause DNA mutations in any targeted cell. In a cancer patient many Genotoxic drugs are given at near lethal doses both singly and in combinations with other cytotoxic drugs to trigger overwhelming DNA mutations and thus trigger cell death. At lower levels, Genotoxic drugs tend to trigger DNA mutations without death.

Cytotoxic drugs are not cancer specific. They can act against any growing cell with the amounts of damage increasing with increased rate of cell growth and the concentration of drug. This means that these drugs do not distinguish between the patient and anyone else. Because they have the greatest concentration of fast growing cells, fetuses, babies and children are the most vulnerable members of our society for DNA damage caused by genotoxic chemotherapy drugs. Unlike adults who have few rapidly growing cells, almost all of fetus's cells are growing rapidly. At high doses genotoxic drugs trigger cell death; at low doses (and even at ultra-low doses) these drugs' actions are skewed towards DNA mutations without death. Within a fetus, these mutations can trigger birth defects and fetal death. Mutations at all early stages of growth (fetus, baby or child) could also cause later cancers or other types of severe childhood diseases with unknown environmental triggers (i.e. Juvenile Idiopathic Arthritis, Juvenile Diabetes, some forms of Autism Spectrum disease).

The dangers of Cytotoxic Chemotherapy drugs have been well understood by the hospitals and medical staff. Employee handling of entire class of drugs is strictly regulated by US Government agencies such as OSHA, NIOSH, and the Joint Commission on Health Care who aim to protect employees from accidental contacts with low levels of these drugs. A recent letter by all three agencies states "Some of these drugs have been known to cause cancer; reproductive and developmental problems, allergic reactions, and other adverse effects that can be irreversible even after low-level exposures."[1] OSHA states that the drugs (after injection into patients) are concentrated in the urine and contaminated clothing and bedding can be a source of exposure. Many of these drugs are known human carcinogens, for which there is no safe level of exposure. It is well documented that some trigger the development of secondary cancer[1].

Post-Patient Drug Danger

Patients receive their chemotherapy drugs in short infusions separated by several weeks. Depending on the type of cancer and its severity, patients may receive 2 to 12 infusions with the course repeated as needed. During each infusion the patients can receive a single drug however with modern protocols (See Figure 1a) the infusion may contain as many as 9 different drugs. 85% of these infusions are done on an outpatient basis. For these, the patient attends the oncology clinic for a few hours, receives their infusion, and returns home.

A number of the drugs received in these cocktails are completely broken down by the patient's body and are not a problem for others or the water supply. However a dangerous few drugs (See Table 1b) are excreted from the patient as the parental drug or active metabolites. These drugs are fully functional even if they are in the patient's sweat, vomit, urine and feces. As the patient and their family dispose of the patient's biologic waste, all are exposed to dangerous amounts of these DNA mutating drugs. As most of the contaminated biologic waste disposal is done through sewer or septic systems, these dangerous drugs enter the wastewater system where they are only partially degraded. One example, cyclophosphamide, is known to survive standard wastewater treatment and may maintain its drug function for months or years[2]. Although these drugs enter the water supply at doses much lower than the therapeutic cancer dose (near lethal levels) their ultralow levels are still a danger to others.

Development Technologies for Measuring Emerging Contaminates – Cytotoxic Drugs

Cytotoxic chemotherapy drugs able to survive a patient's metabolism are not as common as estrogen, heart disease or cholesterol control medication. These common drugs have been found extensively in wastewater, ground water, and even in drinking water and are causing extreme concern. Until recently the inability to tests for the presence of these dangerous cytotoxic drugs led regulators to believe that the levels in wastewater, ground water and drinking water were too low for them to intervene. However new methods are currently being developed to allowed accurate measurements of these dangerous DNA mutating drugs. Previous methods were not sensitive because they could not determine the drug concentrations themselves but observed the apparent amount of damage these drugs could do to selected laboratory cells. Recently, groups in France[3], Germany[4], Czech Republic[5], Croatia[6] and Canada[7] have reported new techniques that combine on-line solid-phase extraction (on-line SPE) coupled with liquid phase chromatography and mass spectrometry (LC-ESI(+/-)-MS/MS) to create sensitive and accurate methods to test for these drugs.

Levels of Genotoxic Drugs in Hospital/Municipal Wastewater as well as Surface Water.

With the development of technologies that can be physically coupled to accurately and sensitively measure the presence of these cytotoxic drugs (on-line SPE coupled with LC-ESI(+/-)-MS/MS), several academic groups have recently published data that demonstrates these cytotoxic drugs are passing from the patients into the hospital sewer system, through municipal wastewater treatment facilities and ending up in surface water. Recent work has followed the passage of cyclophosphamide and its related drug ifosfamide (See Table 2) through all these stages. These two are known to survive advanced biodegradation used in municipal sewage treatment facilities[8]. In addition, they are not removed by many other processes used in standard drinking water finishing processes[2,9]. For that reason they are

assumed to persist in the aquatic environment and to enter drinking water via surface water. In fact cyclophosphamide is usually selected as the reference cytostatic drug to be used to evaluate new methods of eliminating these dangerous chemotherapeutic drugs as well as other drugs from wastewater treatment facilities.

In recent studies cyclophosphamide was found in wastewater exiting German hospitals/cancer facilities[2]. It was also found entering German and Canadian municipal wastewater treatment facilities[10,11]. A study by Buerge et al.[8] evaluated the cyclophosphamide concentrations entering (Influent) and exiting (Effluent) municipal wastewater treatment facilities and demonstrated that these facilities are unable to remove these drugs from the water they treat. In the Montreal facility that handles 50% of the wastewater treated in Quebec, cyclophosphamide was found contaminating the wastewater from one of its two wastewater entry points. When mixed with the other entry point's wastewater, the cyclophosphamide was diluted below the limit of detection (LOD) so could not be measured as the treated water was dumped into the St Lawrence River[8]. However, both of these drugs were discovered in German surface water and in Lake Geneva[8]. In the surface water, the levels were low but sufficient to cause alarm and possibly influence changes occurring in European water policy[2].

Information about other drugs such as 5-Fluorouracil, Doxorubicin and Etoposide and their appearance in wastewater is being determined as the necessary technology is developed (Table 3). Several groups have collected wastewater samples from hospitals and oncology units[3,12,13,14]. This is allowing scientists to determine the amount of these drugs that exit the patients during the few hours they reside in the hospital for their drug infusions. Although some drugs, such as bleomycin are known to exit the body rapidly and would appear in the hospital wastewater, others like doxorubicin would mostly exit the patients after they have returned home. To determine accurate numbers, all of the patients' waste would require several days of collection in the hospital or daily from these septic system.

Predicted Septic System Contamination Results

Another matter for concern is the levels of post-patient cytotoxic drugs that will be found in septic systems and downstream ground water. Significant levels of these dangerous drugs have been found in municipal wastewater treatment facilities and in their treated effluents being released into surface water. These facilities handle the wastewater of only a few contain cancer patients actively excreting hazardous cytotoxic chemotherapy drugs diluted by the wastewater from thousands of non-patient households. This dilution effect does not occur in a septic system. Here all the excreted cytotoxic drugs are concentrated without extensive dilution. Another benefit of a municipal system over a septic system is a municipal system maintains in-line quality testing for immediate intervention when something goes wrong. A household septic system can partially fail without triggering alarm. This would results in even less of the cytotoxic drugs being degraded in the septic tank and more moving into the wastewater diffusion field. From there it can migrate to the ground water and into the local well. Although current research has not yet demonstrated the concentration of cytotoxic drugs in septic system, disturbing data from municipal systems suggest that significant levels of these drugs will accumulate in the septic systems of patients receiving cytotoxic drug infusions.

An addition problem arises in how drinking water may be prepared and delivered. Many users of septic system also obtain their drinking water from local wells instead of large scale municipal systems with advanced drinking water treatment and polishing. With current technologies, it is difficult to predict the danger level of these post-patient cytotoxic drugs to the cancer patient's families and neighbors through their drinking water supply. The German Drinking Water Commission and the Environmental Federal Agency (Germany) have stated that the presence of such strongly genotoxic compounds in drinking water is only allowed if people are exposed for a limited time; if the total amount is restricted; and it avoids exceeding the threshold level of 10 ng/L (Umweltbundesamt (Environmental Agency) 2003)[2,15]. They have added concern for genotoxic and carcinogenic compounds at any level of exposure for more vulnerable members of society for these drugs especially because there is no threshold dose below which no carcinogenic effect may occur.

Risk Prediction

It is difficult to estimate the amount of damage an adult would receive from low doses of cytotoxic drugs in drinking water because many cytotoxic drugs are given at ultra-high (near lethal) levels with infusion repeated 2-12 times. For obvious reasons, the amount of damaged caused by exposure to these drugs at low levels has not been tested. To estimate the relative risk for an adult who has been drinking contaminated water for 70 years, Kümmerer et al.[2] combined data for cyclophosphamide usage in Germany with estimates for the amount of cyclophosphamide passing into drinking water and calculated that this 70 year adult would have received a dose one millionth of the amount given to a patient during their total cancer treatment (all 2-12 infusions combined). The calculations only cover an adult who may not be badly injured by an ultra-low dose. However it is acknowledged that a fetus, baby or child could be disastrously affected by a similar ultra-low dose[2,15].

Reproductive effects associated with occupational exposure to cytotoxic drugs have been well documented. Hemminki et al. 1985[16] found no difference in exposure between nurses who had spontaneous abortions and those who had normal pregnancies. However, the study group consisted of nurses who were employed in surgical or medical floors of a general hospital. When the relationship between cytotoxic drug exposure and congenital malformations was explored and the subject group was expanded to include additional specialties including oncology nurses, there was a 4.7-fold increase in spontaneous abortions for those exposures to cytotoxic drugs of more than once per week.

Non-cytotoxic pharmaceuticals (e.g. estrogen) at low concentration such as the 70 picograms/L found for cyclophosphamide in Lake Geneva may not cause major danger to an adult. However the DNA mutagenic effects of cytotoxic drugs are capable of causing much greater damage. To put their impact in frame of reference, 70 picograms of radioactive iodine (I^{125}) such as that used in thyroid treatments or released in a nuclear plant accident would deliver 1.25 millicuries of radiation. If it was radioactive phosphorus (P^{32}), it would deliver 18.9 millicuries. Although these radiation doses may not cause death in an adult, they would cause damage including the I^{125} destroying the adult's thyroid gland. For a child, the damage could be severe. Although the damage from 70 pg of cyclophosphamide may be less, it could still have disastrous effects for these vulnerable individuals.

Results and their Effects on Public Policy

The European Community bans the discharge of chemicals and metabolites with carcinogenic or mutagenic potential into the wastewater system (Council Directive 80/68/EWG, 1991; Council Directive 76/464/EG, 2000[17]). As the presence of these cytotoxic drugs in wastewater and groundwater become better known, additional regulations will be added. In Switzerland and Germany, there is a movement to prevent hospitals from discharging human waste containing genotoxic compounds into the sewer system[2,12]. To support this, a few European hospitals are developing their own wastewater pretreatment systems to handle oncology patients' waste before it is released into the municipal wastewater treatment system. For example a group in Austria was given sufficient funding to develop a Membrane Bioreactor (MBR) system to pilot cleaning oncology wastewater from an Austrian hospital[12]. The funding covered alteration of the hospital plumbing to divert the wastewater from 3 toilets and 3 showers into the oncology unit into a pilot MBR system sited within the hospital. As hospital wastewater treatment systems are only capturing a small fraction of the post-patient cytotoxic drugs additional technologies is needed to keep these drugs out of the wastewater system and drinking water supply. A cost-effectively method to reduce the number of new technologies needed to remove genotoxics drugs from drinking water is to prevent them from entering the wastewater system.

August 8, 2011, the United States Government Accountability Office released a Report to Congressional Requesters on Environmental Health: Action Needed to Sustain Agencies' Collaboration on Pharmaceuticals in Drinking Water (GAO-11-346[18]). The GAO reported on concerns raised by research results developed by U.S. Geological Survey, EPA, and others concerning pharmaceuticals detected in the nation's drinking water. Although the levels are low and research has not yet defined the extent of human health risk for such exposure, the contamination is a serious concern. At the present time, past research has concentrated on the effects of hormone modulating drugs as well as antibiotics. This report also raised these organizations' concerns about the presence of chemotherapy drugs in the drinking water. Of special attention is the potential for biological effects of long-term, low-dose exposure to cytotoxic drugs in sensitive subpopulations including children and the unborn.

Summary

Cytotoxic chemotherapy drugs are life-saving for cancer patients but can cause disastrous damage to non-patients, especially young members of our society. Unfortunately, a subset of these drugs exits a patient still in their active form. Once in the wastewater system, recently studies have demonstrated these drugs are not completely removed or destroyed. Instead, they pass through the municipal wastewater treatment system into ground water and may migrate intact into the drinking water supply. Efforts need to be made to prevent cytotoxic drugs from entering the wastewater treatment system because this is the safe and cost-effective way to keep them out of the drinking water supply.

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Table 1a. **Drug Combinations for Standard Chemotherapy Protocols.** Expanded details including color legend in Table 1b.

Disease	Protocol	Drugs								
Advanced bladder cancer	MVAC	Doxorubicin	Cisplatin	Vinblastine	Methotrexate					
B cell non-Hodgkin lymphoma	R-FCM	Cyclophosphamide	Mitoxantrone	Fludarabine	Rituximab					
	CHOP-R/ R-CHOP	Cyclophosphamide	Doxorubicin	Vincristine	Prednisone	Rituximab				
Brain tumors	PCV	Vincristine	Procarbazine	Lomustine						
Breast cancer	AC/ CA	Cyclophosphamide	Doxorubicin							
	CAF	Cyclophosphamide	Doxorubicin	Fluorouracil (5-FU)						
	CMF	Cyclophosphamide	Fluorouracil (5-FU)	Methotrexate						
	EC	Cyclophosphamide	Epirubicin							
	FEC	Cyclophosphamide	Fluorouracil (5-FU)	Epirubicin						
Colorectal cancer	FL/ Mayo	Fluorouracil (5-FU)	Folinic acid							
	FOLFOX	Fluorouracil (5-FU)	Oxaliplatin	Folinic acid						
	FOLFIRI	Fluorouracil (5-FU)	Irinotecan	Folinic acid						
Gastric cancer and oesophageal cancer	ECF	Fluorouracil (5-FU)	Cisplatin	Epirubicin						
Lung cancer	CAV	Cyclophosphamide	Doxorubicin	Vincristine						
Hodgkin's lymphoma	ABVD	Doxorubicin	Bleomycin	Vinblastine	Dacarbazine					
	BEACOPP	Doxorubicin	Bleomycin	Cyclophosphamide	Etoposide	Vincristine	Procarbazine	Prednisone		
	ChlVPP/ EVA	Doxorubicin	Etoposide	Vincristine	Procarbazine	Vinblastine	Chlorambucil	Prednisone		
	MOPP	Vincristine	Procarbazine	Mechlorethamine	Prednisone					
	Stanford V	Doxorubicin	Bleomycin	Etoposide	Vinblastine	Vincristine	Mechlorethamine	Prednisone		
	VAPEC-B	Doxorubicin	Bleomycin	Cyclophosphamide	Etoposide	Vincristine	Prednisone			
also leukemia, multiple myeloma	VAMP	Doxorubicin	Vincristine	Methotrexate	Prednisone					
Lymphoma	CBV	Cyclophosphamide	Etoposide	Carmustine						
	EPOCH	Cyclophosphamide	Doxorubicin	Etoposide	Vincristine	Prednisone				
Aggressive lymphomas, neuroblastoma	ICE	Carboplatin	Etoposide	Ifosfamide						
Progressive or recurrent lymphomas	ICE-R	Carboplatin	Etoposide	Ifosfamide	Rituximab					
Multiple myeloma	VAD	Doxorubicin	Vincristine	Dexamethasone						
	Thal/Dex	Thalidomide	Dexamethasone							
Non-Hodgkin lymphoma	COPP	Cyclophosphamide	Vincristine	Procarbazine	Prednisone					
	CHOP	Cyclophosphamide	Doxorubicin	Vincristine	Prednisone					
	m-BACOD	Cyclophosphamide	Doxorubicin	Bleomycin	Methotrexate	Dexamethasone				
	MACOP-B	Cyclophosphamide	Doxorubicin	Bleomycin	Vincristine	Folinic acid	Methotrexate	Prednisone		
	ProMACE- MOPP	Cyclophosphamide	Doxorubicin	Etoposide	Vincristine	Procarbazine	Mechlorethamine	Methotrexate	Prednisone	
	ProMACE-CytaBOM	Cyclophosphamide	Doxorubicin	Bleomycin	Etoposide	Vincristine	Cytarabine	Folinic Acid	Methotrexate	Prednisone
with History of Heart Disease	COP/ CVP	Cyclophosphamide	Vincristine	Prednisone						
Rhabdomyosarcoma	VAC	Cyclophosphamide	Actinomycin	Vincristine						
Testicular cancer	EP	Cisplatin	Etoposide							
	BEP	Cisplatin	Etoposide	Bleomycin						
	VIP	Cisplatin	Ifosfamide	Vinblastine						
Salvage therapy	TIP	Cisplatin	Ifosfamide	Paclitaxel						

Table 1 b. Post-Patient Genotoxic Drugs. Summarized information from FDA approved Patient Package Insets.

Drug	Excretion	Hazards	Related Drugs
Bleomycin	60-70% of active drug in urine < 2 hrs	Birth Defects	
Cisplatin (contains heavy metal platinum)	13-17% intact drug in urine in 1 hr Free platinum in urine at rate relative to drug dose	Seconday cancers Birth Defects Found in Breast Milk	**Carboplatin** **Oxaliplatin**
Cyclophosphamide	5-25% intact drug in urine < 24 hrs Additional cytotoxic and benign metabolites in urine and feces over time.	Secondary cancers, some after many years Birth Defects Sterility	**Ifosfamide**
Doxorubicin	Drug and functional metabolite slow elimination, half-life 20-48 hrs 40% in bile by 5 days 5-15% in urine by 5 day < 3% in urine for up to 7 days Peak breast milk excretion at 24 hrs	Secondary cancers Congestive heart failure Crosses human placenta Birth Defects Early terminations	**Epirubicin**
Etoposide	45% in urine in 5 days Similar % in bile in 5 days	Carcinogen Immune suppression Birth Defects	
Fluorouracil	7-20% active drug by urine < 6 hrs	Cell mutation Birth Defects	
Irinotecan	25-50% in urine and feces in 48 hrs	Cell mutation Birth Defects Can cross placenta	
Mitoxantrone	8% of parent drug in urine in 5 days 16% in bile in 5 days	Secondary leukemia Birth defects Found in Breast Milk up to 28 days	
Trisenox (contains arsenic trioxide, a WWI chemical weapon)	Urine - 15% Arsenic III with additional as methylate metabolites	Known carcinogen Heart abnormalities Birth defects Early terminations	

Table 2. Concentrations of Cyclophosphamide and Related Ifosfamide Contamination in Hospital/Municipal Wastewater and Surface Water

Source Location			Sample Concentration		Reference
			Cyclophosphamide	Ifosfamide	
Hospital WW					
	Freiberg University Hospital German cancer facility- Freiberg		<LOD - 40 ng/L	<LOD - 2060 ng/L	Kümmerer et al. 2010
Municipal WW					
	Germany		146 ng/L	24 ng/L	Steger-Hartmann et al. 1996
	Montreal, Canada [1]	*Influent from south*	9 ng/L		Garcia-Ac et al. 2008
		Influent from north	<LOD		
		Effluent (total	<LOD		
	Zurich Werdholzli, Switzerland[2]	*Influent*	2-5 ng/L	1.4 - 5 ng/L	Buerge et al. 2006
		Effluent	2.1 - 4 ng/L	1.7 - 6 ng/L	
	Mannedorf, Switzerland[3]	*Influent*	11 ng/L		
		Effluent	10 ng/L		
	Wadenswil, Switzerland[4]	*Influent*	6 ng/L		
Landfill Effluent					
	Stuttgard, Germany		97-192 ng/L	32-42 ng/L	Jjemba 2008
Surface Water					
	Germany		0.6-0.7 ng/L	0.6-1 ng/L	Kümmerer et al. 2010
	Lake Geneva		0.07 ng/L	0.05 ng/L	Buerge et al. 2006
	Limmat at outflow of Lake Geneva		0.05 ng/L	0.05 ng/L	
	Limmat downstream WWTP, Lake Geneva		0.15 ng/L	0.08 ng/L	

Both cyclophosphamide and ifosfamide are metabolized to the active compound 4-hydroxy-oxazaphosphorine metabol

Neither cyclophosphamide and ifosfamide are noticibly degraded in wastewater treatment nor removed in standard drinking water finishing process

1 - Handles 50% of wastewater treated in Quebec; 7.6 Mm^3/day

2 - Handles wastewater from large city (Zurich) with several oncology hospitals; 0.19 - 0.32 Mm3/day

3 - Handles wastewater from city (Mannedorf) with one specialty oncology hospital; 0.015 Mm3/day

4 - Handles wastewater from small city (Wadenswil) with no oncology hospitals

all use 3 or 4 stage (mechanical, biological, chemical and filtration)

Table 3. Wastewater Contamination by Non-Cyclophosphamide Post-Patient Genotoxic Drugs

Drug	City	Source		Protocol	Conc in Wastewater	Hospital Use	Reference
5-Fluorouracil (5-FU)	Vienna, Austria	Wastewater	Section of Oncology Ward	Outpatient*	<8.6 - 123.5 ug/L	1.8 - 6.1 gm administered/day	Mahnik et al. 2007
	Switzerland	Wastewater	Large Canton Hospital (1% of Swiss beds)	Outpatient	<5 - 27 ng/L	0 - 5 patients/day	Weissbrodt el al. 2009
	Paris, France	Wastewater	French Hospital	Outpatient	0.09 - 4 ug/L	12/14 samples tested	Mullott et al. 2009
	Bejing, China	Wastewater	21 Bejing Hospitals	Inpatient?	42 ng/L		Yin et al. 2010
Doxorubicin	Vienna, Austria	Wastewater	Section of Oncology Ward	Outpatient**	<0.26 - 1.35 ug/L	16.8 - 244 mg administered/day	Mahnik et al. 2007
	Bejing, China	Wastewater	21 Bejing Hospitals	Inpatient?	<LOD		Yin et al. 2010
Etoposide	Bejing, China	Wastewater	21 Bejing Hospitals	Inpatient?	42 ng/L		Yin et al. 2010

* Patients treated in outpatient unit and immediately sent home

** Slow drug elimination from tissues causes little excretion during patients hospital stay.

**Most drug elimination would occur at home.