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Antineoplastic drugs in surface waters: presence, exposure, and risk.

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Abstract Antineoplastic drugs are highly toxic pharmaceuticals used during chemotherapy. Their presence in surface waters has been reported worldwide, increasing environmental and human health concerns. This work estimates the risks from the exposure of humans to antineoplastic drugs via surface waters in a worldwide perspective. Three different scenarios were considered: (i) dermal contact with surface waters, (ii) accidental ingestion of surface waters and (iii) drinking potable water captured from rivers, assuming no further degradation. All but tamoxifen, for which an extraordinarily high average dermal absorbed dose (AD_{abs}) was found, the AD_{abs} were always lower than the average daily potential dose (ADD), whether ingested inadvertently or voluntarily (potable water produced from contaminated surface water). To determine whether there would be any risk for humans from their exposure to antineoplastic drugs, the AD_{abs} and ADD were contrasted with the Permitted Daily dose (PDE). The third exposure scenario revealed these compounds' presence in worldwide surface waters could represent a risk to children, if the highest concentration reported worldwide for cyclophosphamide in surface waters is considered. Even for the remaining antineoplastic drugs/exposure settings, health hazards might arise from synergistic effects and/or prolonged exposures.

Keywords: surface waters, cytotoxics, cytostatic drugs, risk assessment, human exposure.

1. Introduction

All around the world, the prevalence of cancer is rising every year. By 2040, the International Agency for Research on Cancer projects an average yearly incidence of 30.2 million new cases of cancer, 1.67 times today's rate [1].

Antineoplastic drugs' prescriptions increase with the likelihood of a cancer diagnosis, since these are pharmaceuticals used in chemotherapy [2]. Antineoplastic medications, like all other pharmaceuticals, are not completely metabolized by the human body: a portion of the administered dose is eliminated in the urine and feces. Most antineoplastic medications (and their metabolites) are poorly or non-degraded in conventional wastewater treatment facilities, allowing them to reach surface and ground waters, which can endanger aquatic life as well as the environment as a whole and humans [3, 4].

Details about the presence of antineoplastic medications in surface waters is not much globally. Generally, relatively low concentrations (ng/L) are detected, typically ranging from not detected to some extreme values (such as 1.9 µg/L for cyclophosphamide) [5].

In a recent work, our research team estimated the risk associated with aquatic organism exposure to antineoplastic medicines based on concentrations reported in surface waters worldwide [6]. Five antineoplastic drugs were identified as of most concern: tamoxifen, bicalutamide, methotrexate, mycophenolic acid and tegafur [6]. In addition, Borgatta and colleagues demonstrated that the presence of tamoxifen at relevant environment concentrations had an impact on the size, viability, reproduction, and intrinsic rate of natural expansion of four generations of the microcrustacean *Daphnia Pulex* [7]. There is currently no information available regarding the effects that those levels of antineoplastic drug concentrations in surface waters might pose to humans. Some antineoplastic drugs were classified as "hazardous/dangerous substances" and Material Safety Data Sheets report infertility, heritable genetic damage and even cancer as some of the possible consequences of exposure to some of these compounds

[8]. This is of paramount relevance and stands as the major goal of the current work because some of these pharmaceuticals—such as chlorambucil, cyclophosphamide, etoposide, and tamoxifen—have already been identified as human carcinogens by the International Agency for Research on Cancer.

Three different scenarios were considered to estimate the risks from the exposure of humans to antineoplastic drugs via surface waters: (a) by cutaneous contact with contaminated water, (b) through inadvertent intake of contaminated water and (c) by drinking potable water over an extended period (considering that the potable water is produced through river water capture, assuming negligible antineoplastic drug degradation in water treatment facilities). Global reported concentrations of antineoplastic drugs (obtained from the literature) were used for exposure determination and risk assessment.

2. Materials and methods

Human exposure to antineoplastics was estimated for children (7–10 and 11–14 years old) and adults (men and women) to examine how the contamination affected different targets.

Several factors such as compounds concentrations (C_{medium}, ng/L), water ingestion rate (*IngR*, L/day), the body's exposure duration (*ED*, years), frequency (*EF*, events/year), the body weight (*BW*, kg), averaging time (*AT*, days), the skin surface area (*AS*, cm^2) and compounds permeability coefficient (*kp*, cm/h) were considered for exposure calculations. These variables were determined based on information from the EPA's Exposure Factors Handbook [9].

2.1. Exposure by dermal absorption

The exposure to antineoplastic drugs by dermal absorption of contaminated water was calculated as follows:

$$AD_{abs} = \frac{DA_{event} \times AS \times EF \times ED}{BW \times AT} \times 10^9 \qquad \text{Eq. 1}$$

Being DA_{event} the absorbed dose (mg/cm^2-event), calculated by the product of the permeability coefficient (*kp*, cm/h), the concentration of antineoplastics in water contacting skin (mg/cm^3) and the time of contact (t, hr/event), which was considered to be 1.3 h for adults, 2.3 h for children aged between 7 and 10 years old, and 1.7 h for children aged between 11 and 14 years old. *ED*, years, is the body's exposure duration (30 years for both adults and 4 years for both children); *EF*, events/year, the frequency (120 events/year both for adults and children); *AS* and *BW* (kg and m^2) being, respectively, 1.94 m^2 and 71.8 kg for men, 1.69 m^2 and 65.4 kg for women, 1.42 m^2 and 48.2 kg for older children (11–14 years old) and 1.04 m^2 and 30.2 kg for younger children (7–10 years old); finally, *AT* was set for the human life expectancy of 78 years old [10].

2.2. Exposure by Ingestion

The exposure to antineoplastic drugs by ingestion of contaminated water while swimming was calculated as follows:

$$ADD = \frac{C_{medium} \times IngR \times EF \times ED}{BW \times AT} \times 10^9 \qquad \text{Eq. 2}$$

Where C_{medium}, ng/L, is compounds maximum concentration found and *IngR*, L/day, the water ingestion rate (0.04 L/day for men, 0.03 L/day for women, 0.11 L/day for older children and 0.08 L/day for younger children). The remaining parameters were the same as used in previous section.

Eq. 2 was employed in the estimation of the human exposure to antineoplastic drugs through long-term intake of polluted drinking water. Since this scenario is expected to happen during a whole lifetime, then Eq. 2 is resumed to Eq. 3:

$$ADD = \frac{C_{medium} \times IngR}{BW} \times 10^9 \qquad \text{Eq. 3}$$

In this case, the *IngR* values considered were 1.43 L/day for men, 1.31 L/day for women, 0.77 L/day for older children and 0.63 L/day for younger children.

2.3. Risk Assessment

The Permitted Daily Exposure (PDE), in µg/day, was determined for each antineoplastic drug in order to interpret the exposure results. If the $PDE > ADD$ or AD_{abs}, then there is no risk anticipated; if the $PDE < ADD$ or AD_{abs}, then there may be a risk to human health. PDE was calculated as follows [11]:

$$PDE = \frac{NOAEC \times weight\ adjustment}{F1 \times F2 \times F3 \times F4 \times F5} \qquad \text{Eq. 4}$$

where NOAEC is the No Observed Adverse Effect Concentration, the weight adjustment is an arbitrary human body weight of 50 kg for adults and 10 kg for children [12], and F1, F2, F3, F4 and F5 are modifying factors, which depends on the toxicological information available for each drug.

3. Results and discussion

3.1. Exposure by dermal absorption

When swimming in contaminated rivers, the average daily absorption rate (AD_{abs}) of antineoplastic drugs is in the pg/kg range, with an average of 17.2 pg/kg-day for all antineoplastic drugs. Although concentrations play a major role in final AD_{abs} values, *kp* also highly interferes with exposure parameters. The compound with the highest absorption dose was tamoxifen (58.5–420.4 pg/kg-day). Analyzing the results, men absorb via dermal around 1.04 times more than women, 3.33 times more than children ageing between 7 and 10 years old and 5.26 times more than older children (11–14 years old). Figure 1-A represents the AD_{abs} obtained.

3.2. Exposure by Accidental Ingestion of River Water

The average daily potential dose (ADD) due to accidental ingestion of water while swimming in rivers is also relatively low for both adults and children. Even though younger children (ingestion rate of 0.11 L/day) consume more water than older children (0.08 L/day) and significantly more than adults (0.04 L/day for men and 0.02 L/day for women), men have higher ADD values (average of 19 pg/kg-day for all antineoplastic drugs) due to their longer exposure duration (ED) and exposure frequency (EF), which are factors in ADD calculation. Regarding the antineoplastic drugs, the one for which a higher average daily potential dose was calculated was cyclophosphamide (56–127 pg/kg-day). Figure 1-B shows a schematic representation of the results obtained.

3.3. Exposure by long-term drinking water

Regarding the ingestion of drinking water produced from river water capture (assuming no further degradation of antineoplastic drugs), the ingested dose of antineoplastic drugs is higher than the absorbed dose via dermal and the accidental ingestion dose while swimming, for adults and children. Cyclophosphamide was once more the antineoplastic with the largest exposure potential (30512 - 40047 pg/kg-day), as it was discovered in surface waters at higher quantities than the other antineoplastics. Generally, younger children are those with higher ADD (average of 6027 pg/kg-day), followed by men and women, who have similar ADD (5740 pg/kg-day), and older children (4592 pg/kg-day). Figure 1-C shows a schematic representation of the results obtained.

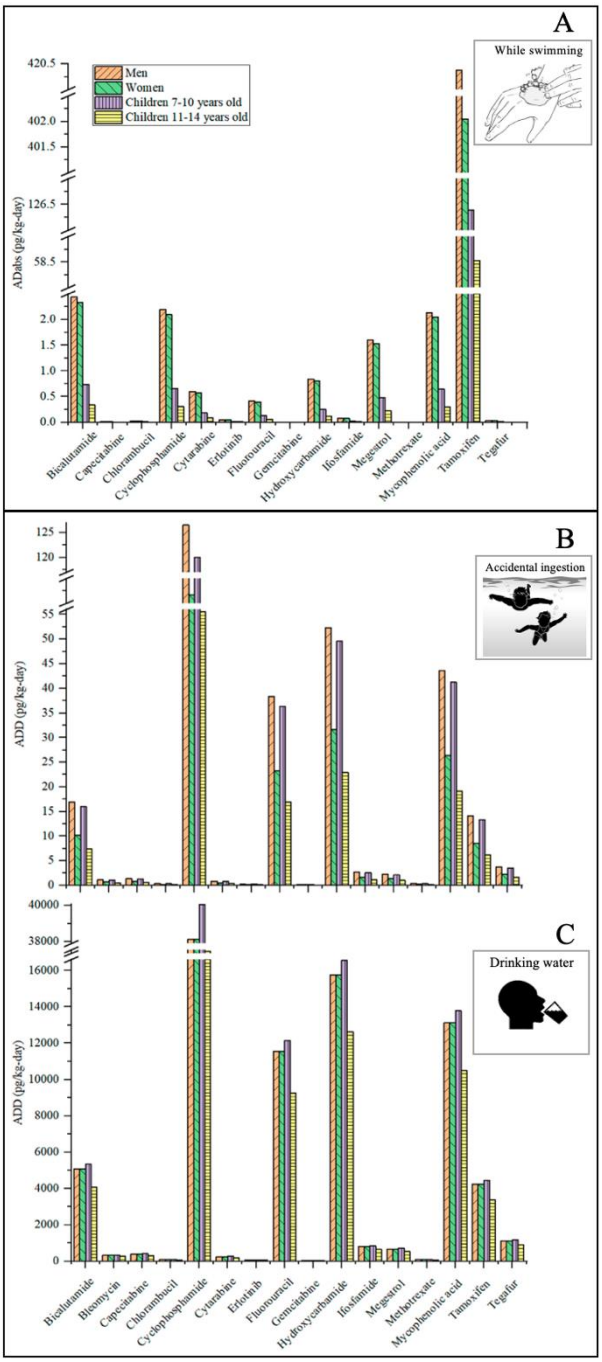

Figure 1 - Human absorption doses of antineoplastic drugs via (A) dermal exposure while swimming, (B) accidental water ingestion while swimming and (C) drinking water.

3.4. Risk Assessment

The mean PDE values for adults and children are roughly 3873 and 775 μg/day, respectively, and 25% to 75% of the values fall between the range of 10-350 μg/day for adults and 2-70 μg/day for children. Tamoxifen had the lowest PDE (1 μg/day for children and 3 μg/day for adults), followed by cyclophosphamide, doxorubicin, and gemcitabine (1 μg/day for kids and 5 μg/day for adults). Capecitabine was the drug with the highest PDE (75000 μg/day for adults and 15000 μg/day for children).

Most of the studied scenarios lead to no risk at a long-term (PDE values above the AD_{abs} and ADD values). The dermal absorption and unintentional intake of

contaminated water did not indicate any potential concern. However, when surface water is contaminated with cyclophosphamide at the greatest concentration ever recorded, drinking potable water produced from it could represent a risk for children (the ADD is 1.2–1.5 times higher than the PDE, for both ages). Since this highest concentration could be an exception, the PDE was also compared to the ADD computed from the second-highest cyclophosphamide concentration ever recorded in the literature for surface waters, 65 ng/L [13]. It was then found that drinking water does not likely represent a risk to humans, using this concentration. It is important to emphasize that cyclophosphamide was already classified as a carcinogenic to humans by the International Agency for Research on Cancer [14], thus any concentration of this antineoplastic drug in waters should not be disregarded.

4. Conclusions

The exposure of humans to antineoplastics while swimming in rivers (via dermal absorption or accidental ingestion) was predicted, as well as the exposure associated with the long-life consumption of drinking water produced from river water capture (assuming no further degradation of antineoplastic drugs). Except for tamoxifen, for which an extraordinarily high average dermal absorbed dose (AD_{abs}) was found, the AD_{abs} were always lower than the average daily potential dose (ADD).

In order to determine whether there would be any risk for humans from exposure to antineoplastic drugs under these contexts, the AD_{abs} and ADD were contrasted with the PDE. Drinking potable water may put childrens at risk if it is contaminated with cyclophosphamide at the highest concentration ever recorded for surface waters. Dermal absorption and accidental ingestion of contaminated water during swimming did not reveal any potential risk. However, health hazards from synergistic effects and/or prolonged exposures should not be ruled out.

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