

Correlation between Trihalomethanes and the Development of Bladder Cancer

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Correlação entre Trihalometanos e o Desenvolvimento do Câncer de Bexiga

Correlación entre Trihalometanos y el Desarrollo del Cáncer de Vejiga

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ABSTRACT

Introduction: The trihalomethanes (THM) are one of the by-products created from the chlorination process, the most applied technique for water disinfection. Since the first time they were reported in 1974, studies attempted to find a positive correlation between human's exposure to THM and cancer. **Objective:** Review the available scientific literature reported about the presence of THM in drinking water's treatment and its relation with the carcinogenic process of bladder cancer. **Method:** The present study consists of an integrative literature review. The articles were searched in the ScienceDirect and PubMed databases utilizing the following keywords obtained from the Subject Descriptors in Health Science (Virtual Health Library): "trihalomethanes", "disinfection by-products" and "bladder cancer". **Results:** In total, 31 articles were selected for this review, most of them published in environmental or toxicological journals. The authors analyzed descriptive studies, meta-analysis and other experimental studies, finding a positive, but controversial relationship between the THM exposures, specifically the chronic, and the carcinogenic process associated with many pathological mechanisms. **Conclusion:** The studies recognized the potential risk of the THM exposure in humans, however, more evidence is needed for a better understanding of THM's toxicological aspects and the influence of other health risk factors in the carcinogenicity process.

Key words: Trihalomethanes; Disinfection By-Products; Urinary Bladder Neoplasms.

RESUMO

Introdução: Os trihalometanos (THM) constituem um grupo de subprodutos gerados pela desinfecção da água por meio da cloração. Desde a primeira vez em que foram reportados, em 1974, são alvo de estudos que buscam estabelecer uma relação positiva entre a exposição dos humanos a esses compostos e o desenvolvimento de câncer. **Objetivo:** Revisão da literatura científica disponível sobre a presença de THM na água e sua relação com o desenvolvimento do câncer de bexiga. **Método:** Levantamento bibliográfico da revisão feito nas bases de dados *ScienceDirect* e *PubMeb*. Os descritores utilizados foram "trihalomethane", "disinfection by-products" e "bladder cancer" dos Descritores em Ciências da Saúde (DeCS) da Biblioteca Virtual em Saúde. Os artigos selecionados foram publicados nos últimos cinco anos. **Resultados:** A amostra final desta revisão foi constituída por 31 artigos, sendo a maioria deles publicados em jornais e revistas sobre meio ambiente. Analisaram-se estudos descritivos, metanálises e outros estudos individuais com delineamento experimental, encontrando uma associação positiva, mas controversa, entre os THM e o câncer, associada a diferentes mecanismos. A relação mais consistente tem sido entre a exposição crônica e o câncer de bexiga. **Conclusão:** Os estudos reconhecem que existem riscos significativos à saúde relacionados aos THM, no entanto, evidências que esclareçam os mecanismos de ação e o papel que outros fatores de risco possuem, juntamente com os THM, ainda permanecem incertas.

Palavras-chave: Trihalometanos; Subprodutos da Desinfecção; Neoplasias da Bexiga Urinária.

RESUMEN

Introducción: Los trihalometanos (THM) constituyen un grupo de subproductos generado por la desinfeción del agua mediante cloración. Desde la primera notificación en 1974, son objeto de estudios que buscan establecer una relación positiva entre la exposición humana a estos compuestos y el desarrollo de cáncer. **Objetivo:** Revisión de la literatura científica disponible sobre la presencia de THM en la agua y su relación con el desarrollo del cáncer de vejiga. **Método:** El estudio bibliográfico de la revisión se realizó en las bases de datos *ScienceDirect* y *PubMeb*. Los descriptores utilizados fueron "trihalomethane", "disinfection by-products" e "bladder cancer" – de Descriptores de Ciencias de la Salud (DeCS) de la Biblioteca Virtual en Salud. Los artículos seleccionados han sido publicados en los últimos 5 años. **Resultados:** La muestra final de esta revisión consistió en 31 artículos, la mayoría publicados en periódicos y revistas ambientales. Se analizaron estudios descriptivos, metaanálisis y otros estudios individuales con diseño experimental, encontrando una asociación positiva, pero controvertida, entre los THM y el cáncer asociado con diferentes mecanismos. La relación más consistente ha sido entre la exposición crónica y el cáncer de vejiga. **Conclusión:** Los estudios reconocen que existen riesgos significativos para la salud relacionados con los THM, sin embargo, las pruebas que aclaran los mecanismos de acción y el papel que otros factores de riesgo tienen, junto con los THM, siguen siendo inciertos. **Palabras clave:** Trihalometanos; Subproductos de la Desinfeción; Neoplasias de la Vejiga Urinaria.

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INTRODUCTION

The low quality of the water is an important human health issue faced by the societies due to the possibility of spreading diseases that can affect the individuals in an epidemic scale¹. Several water treatment technologies were developed to solve this sanitary problem over the years – disinfection by chlorine was one of them¹.

Chlorination stands out as the water disinfection method most utilized because of its simplicity, low cost, and efficacy. When combined with filtration, chlorination systems reduce remarkably water transmitted diseases and the surges of communicable gastrointestinal diseases disappear when these processes work as designed². Nevertheless, chlorine for disinfection reacts with organic and inorganic matter, forming the disinfection byproducts (DBP)³.

The first class of DBP reported in 1974 was trihalomethanes (THM). Since then, more than 700 DBP were identified, the main are: haloacetic acids (HAA), halo acetonitrile (HAN) and THM⁴. The nature and concentration of DBP formed in drinking water depend on the conditions of disinfection and composition of the source⁵. The diversity of DBP encountered in water is due to the reaction of organic matter with chemical components of the disinfection processes giving rise to a complex mixture of organic compounds characterized by different molecular weights and chemical functionalities. Therefore, the composition of these disinfection byproducts varies according to the composition of the water, pH and other factors as season and climate⁵. THM are the most common and dominant class of DBP contributing with 10-20% in the composition of chlorinated water⁶. They are the most investigated compounds due to its high prevalence and concentration⁷.

The reports in the literature established a close relation between THM exposure, specifically the chronic and its adverse effects as after the absorption, these elements tend to bioaccumulation and mutagenicity, resulting in carcinogenic effects. For this, they are frequently reported in literature as potential carcinogenic with strong relation with bladder cancer and occasionally, but with lower prevalence, with colon and rectum cancer^{7,8}.

The most consistent association has been with bladder cancer, one of the prevalent neoplasms of the urinary tract. With estimates of nearly 60 thousand new cases per year, bladder cancer is one of the most frequent among American men – after skin, prostate, colon and lung^{9,10} cancer. In Brazil, the number of new cases of bladder cancer estimated for each year of the triennium 2020-2022 will be of 7,590 cases in men and 3,050 in women¹¹.

Given its generalized occurrence, the potential impacts to human health and the toxicity associated with the exposure to THM are of special interest because of its carcinogenic potential. Understand the implications of this emerging issue for human health is crucial for the development of more effective hydric safety plans¹². The main goal of this article is to review the scientific literature available about the presence of THM in water in its relation with the development of bladder cancer.

METHOD

The study consists in an integrative review through search in the databases ScienceDirect and PubMed. The first stage was the elaboration of the research question: “Do THM correlate with the development of bladder cancer?”. The second stage addressed the search and selection of the studies applying the following Descriptors of Sciences of Health (DeCS): “trihalomethane” AND “disinfection by-products” AND “bladder cancer” and applied the filter of last 5-years publications. 192 articles, thesis, dissertations, book chapters, experimental studies, meta-analyzes and other reviews were found, only one was duplicate. Of the remaining 191, 43 were selected after reading the abstract. From the full reading and after applying the exclusion criteria complete text not found, articles addressing carcinogenesis of neoplasms other than bladder and articles published in languages different from Portuguese or English, 19 articles remained for literature review.

At the end of the search and selection of the studies, another nine articles were included in compliance with the inclusion criteria: last five years (2015-2020), full text and articles in English and Portuguese. In total, 28 articles were reviewed for the third stage characterized by data collection (Figure 2). For the fourth and fifth stages, the content of the articles was reviewed critically and henceforward, the synthesis and discussion of the results. At last, the sixth and seventh stages consisted in the presentation of the complete integrative review shown in Figure 1.

RESULTS

The final sample of this review consisted of 28 articles published in environmental journals and magazines in the whole world in great number in the United States, China and Spain followed by Australia, Canada, South Korea, Portugal, India, Turkey, South Africa, and France. After the critical analysis of the articles enrolled, the main results per year of publication are shown in Chart 1.

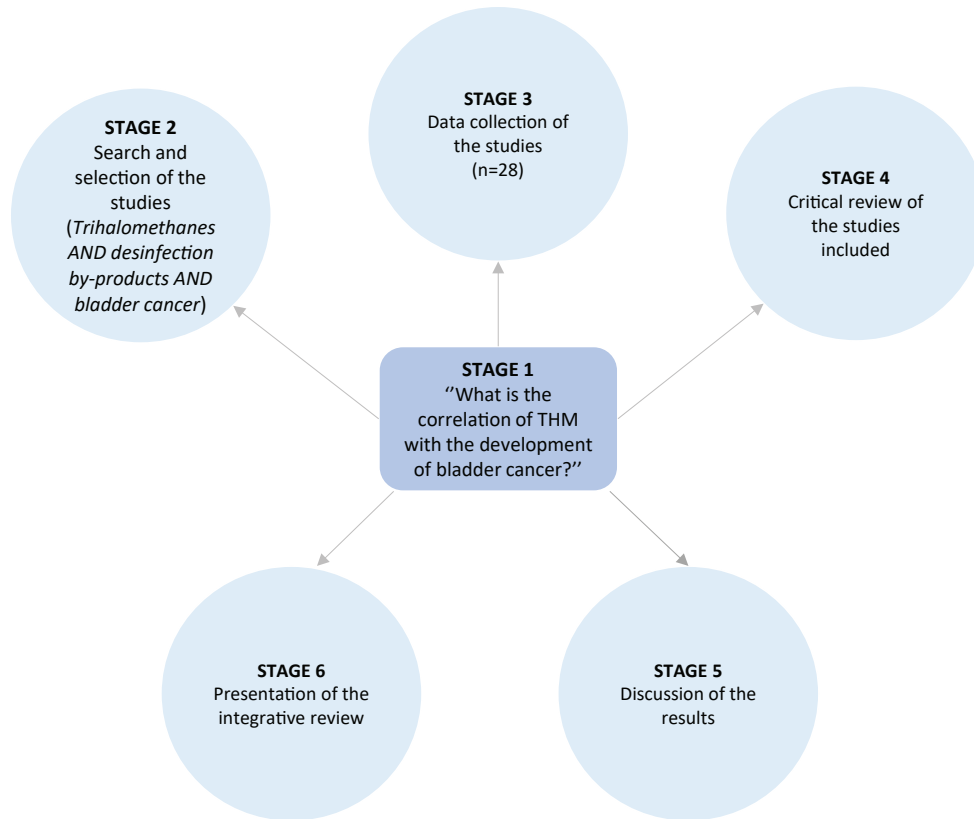


Figure 1. Stages of the integrative review
 Source: Adapted from Mendes et al.¹³.

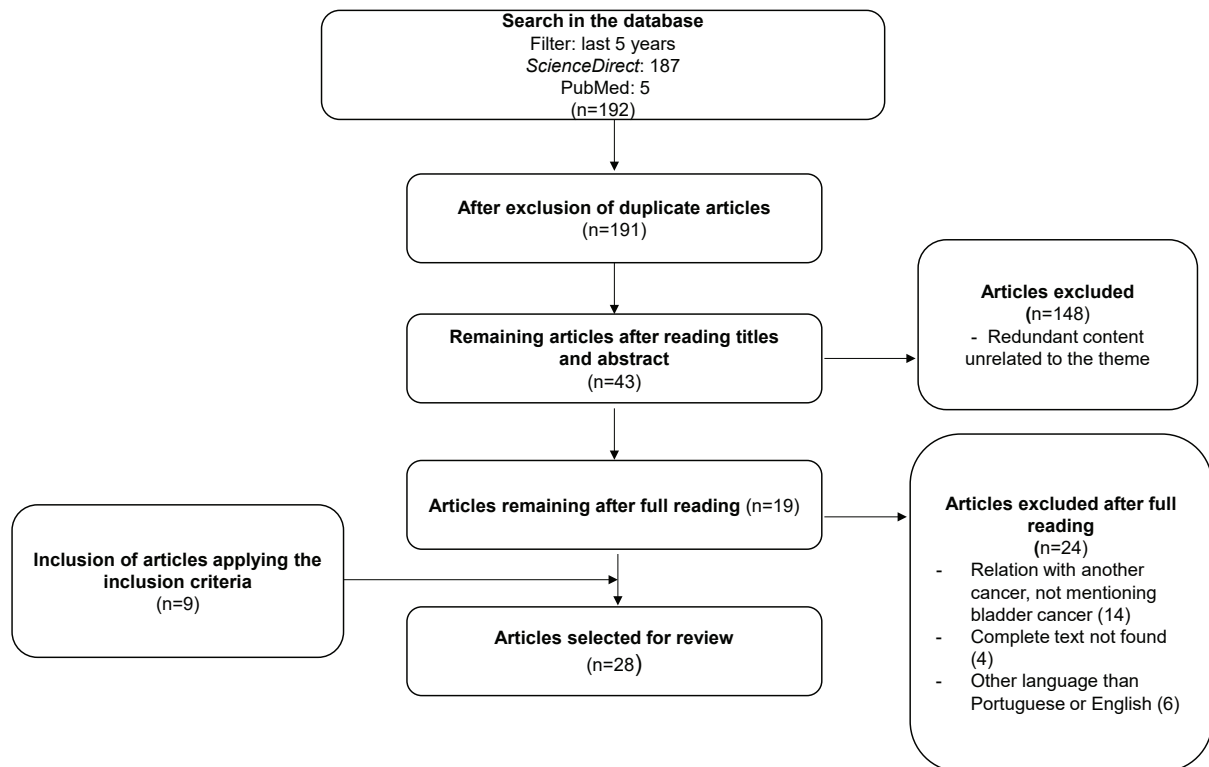


Figure 2. Flowchart with the study stages

Chart 1. Summary of the THM and DBP effects in the development of bladder cancer

Article	Method	Authors/year	Results
<i>Epidemiology of bladder cancer</i>	Review extracted from the chapter of the book "Bladder cancer, an issue of hematology/oncology clinics of North America"	Malats and Real, 2015	It was found a positive association among the byproducts of water chlorination (OR: 1.24; 95% CI 1.09-1.41) and urothelial bladder cancer. The prevalence is in men exposed to a mean of 1 ug/L (particles per billion) of THM. No association was reported for women – the author suggests that the discrepancy of these results can result from the geographical differences among the European countries: France, Finland and Spain and the USA countries, US, and Canada
<i>Overview of disinfection By-products and Associated Health Effects</i>	Literature review	Villanueva et al., 2015	In humans, there was a positive reaction with bladder cancer due to exposure to a concentration of THM > 49ug/L together with the presence of polymorphism of CYP2E1 (OR: 2.0; 95% CI (1.1-3.9)). In relation to brominated THM, metabolism is altered through GSTT1 (OR: 1.8; 95% CI 1.1-3.1) which generates carbonyl-reactive molecules targeting DNA observed in in vitro studies
<i>Assessing the human health impacts of exposure to disinfection by-products - A critical review of concepts and methods</i>	Literature review	Grellier et al., 2015	Unregulated DBP have bigger carcinogenic risk than THM and HAA. As more unregulated DBP studies appear, the relevance of THM as carcinogenic agents will decrease. However, reinforces the positive association between exposure to THM and bladder cancer in men while evidences that other DBP are related to other cancers are not found
<i>Mutagens</i>	Review published in chapter of the book "Encyclopedia of Food and Health"	Schrader, 2003	Disinfection with chlorination processes produces mutagens of chlorinated compounds, the most potent is 3-chlorine-4-(diclometil)-5-hidroxi-2-(5H)-furanone. The brominated THM were the compounds most related with mutation processes
<i>Blood trihalomethane levels and the risk of total cancer mortality in US adults</i>	933 adults without history of cancer were evaluated according to the concentrations of THM in the blood in parallel with the analysis of the causes of death listed in the "International Classification of Disease 10 th Revision"	Min and Min, 2016	There was more prevalent positive relation in adults between 40 and 59 years of age with elevated serum levels of dibromochloromethane, bromoform and brominated THM in general. The risk of mortality by neoplasms in those adults was approximately 4-fold bigger than those unexposed to these substances or who had low level of exposure
<i>Occurrence, origin, and toxicity of disinfection byproducts in chlorinated swimming pools: an overview</i>	Literature review	Manasfi et al., 2017	There was an increase of the risk of bladder cancer among participants exposed to THM in swimming OR: 1.5 (95% CI 1.18-2.09) and shower/bath OR: 1.83 (95% CI 1.17-2.87). Dermal route accounted for 94.2% of total exposure to THM for swimmers
<i>Occurrence and formation of disinfection by-products in the swimming pool environment: a critical review</i>	Literature review	Carter and Joll, 2017	Inhalation is considered as the main route causing mutagenicity, cancer risk is 3-fold bigger than by intake or dermal absorption. The existing regulation may not be as much comprehensive to analyze health risks associated with DBP in swimming pools because inhalation occurs more frequently than intake and there is high concentration of DBP in swimming pools in comparison with filling waters
<i>Disinfection byproduct regulatory compliance surrogates and bromide-associated risk</i>	Cross-sectional observational study	Kolb et al., 2017	The study indicates that the THM regulation based in the values of the sum of the class TTMH do no cover correctly the risk because different species have different risks

to be continued

Chart 1. continuation

Article	Method	Authors/year	Results
<i>Gene expression changes in blood RNA after swimming in a chlorinated pool</i>	The volunteers swam for 40 minutes in the pool. Blood samples were collected and 4 types of THM (chloroform, bromodichloromethane, dibromochloromethane and bromoform) were measured in the air exhaled after swimming. To evaluate the intensity of the physical exercise, metabolic equivalent were measured and for the evaluation of the gene, it was utilized IlluminaHumanHT-12V3. Linear and mixed models were utilized to identify the relation between the changes of the genic expression and exposure to THM	Salas et al., 2017	There was significant change in the genic expression of the volunteers in the short term – measured from the increase of THM exhaled and quantification of the metabolic rate after swimming in chlorine treated pools. Notwithstanding, the study affirms it was unable to differentiate whether the change is actually related to exposure to DBP
<i>Bladder cancer and water disinfection by-product exposures through multiple routes: a population-based case-control study (New England, USA)</i>	UK case-control study, being n=1,213 cases and n=1,418 controls. The study estimated the exposure to THM during the lifetime through the following routes: intake, shower, and hours of swimming pool. At last, the odds ratio was calculated with CI 95%, considering non-conditional logistic regression for confounding factors of the results	Beane Freeman et al., 2017	Reasonable association between bladder cancer and daily average intake and cumulative exposure of 5% THM was found with greater exposure, specially concentrations above 45ug/L. This study has also shown a positive similar relation both for men and women, different from other studies reporting stronger evidence in men. No positive relation was found in hours of use of swimming pool
<i>Multi-route - Multi-pathway exposure to trihalomethanes and associated cumulative health risks with response and dose addition</i>	Observational, longitudinal study estimating the cumulative risks of exposure to THM by multiple routes with response and dose addition methods	Genisoglu et al., 2019	Carcinogenic risk of THM related to each route of exposure was estimated in this study. The values of cumulative risks were divided in 4 categories: no risk (safe zone), zone of acceptable risk, zone of low priority and unacceptable risk (high priority). Values ranging from safe zone to low priority were found for routes of intake and inhalation while the values of cutaneous exposure were estimated for the safe zone
<i>Genotoxicity of disinfection byproducts and disinfected waters: a review of recent literature</i>	Literature review	Cortés and Marcos, 2018	THM tested positive for DNA-break induction from the comet assay. However, the test detects damages usually repaired in the short-term by cells, so genotoxicity data more relevant to persistent mutations are necessary. The study mentions that polymorphisms in some enzymes (GSTT1, GSTZ1 and CYP2E19) modified the risk of bladder cancer associated with DBP
<i>Blood transcriptional and microRNA responses to short-term exposure to disinfection by-products in a swimming pool</i>	Longitudinal, observational study evaluated the genic expression of the whole genome and the microRNA of blood samples collected from 43 volunteers before and 2h after 40 minutes of swimming in a chlorinated pool	Espín-Pérez et al., 2018	A total of 1,778 transcriptions were associated with exposure to THM. Nine genes expressed can be linked to bladder cancer because they are involved in routes related to cancer processes. Thus, it was seen that short-term exposure to DBP through swimming in pools can be indicative of increased risk of bladder cancer ($p=0.227$)

to be continued

Chart 1. continuation

Article	Method	Authors/year	Results
<i>Drinking Water Disinfection Byproducts (DBPs) and human health effects: multidisciplinary challenges and opportunities</i>	Literature review	Li and Mitch, 2018	The study investigates whether the regulation and researches are targeted to the correct compounds since THM and HAA correspond to only 10% of total organic halogen present in chlorinated waters. Results indicate that classes of unregulated DBP are orders of magnitude more cytotoxic and genotoxic than the regulated. Even if factors of toxicity have been identified, they should be incorporated to retrospective studies of epidemiology of cancer, evaluating its concentrations in past decades as well as its time-space variations
<i>Heterogeneity in the relationship between disinfection by-products in drinking water and cancer: a systematic review</i>	Systematic review	Benmarhnia et al., 2018	Reinforces the relation between CYP2E1 in the metabolism of the chlorophorm as well of the glutathiones in the metabolism of the brominated THM and the carcinogenic processes. The role of these enzymes can be critical to understand the motive by which bladder cancer related to THM is more prevalent in men because it is more pronounced in this gender. However, the study concludes there are still scarce evidence to consider not only sex-related disparities and also related to socioeconomic differences
<i>Hazard and mode of action of disinfection by-products (DBPs) in water for human consumption: evidences and research priorities</i>	Literature review	Chaves et al., 2019	According to the review the evidence of the association between the exposure to DBP and cancer was inconsistent to confirm that this association is causal because most of the DBP identified continues with unknown biologic activities. In addition, it is emphasized the importance of the analysis of unregulated DBP as they demonstrate to be more genotoxic and cytotoxic than some regulated compounds as the THM
<i>Application of biomarkers in the study of the health effects of disinfection by-products</i>	Literature review	Chen et al., 2019	Analysis of the application of biomarkers in the study of the health effects of DBP, concluding there is no specific marker proving the relation of the mixture of DBP with the development of health problems
<i>Carcinogenicity of disinfection byproducts in humans: epidemiological studies</i>	Review extracted from "Encyclopedia of Environmental Health - 2nd edition"	Villanueva, 2019	The studies demonstrated positive evidence in relation to bladder cancer alone. However, data still continue controversial due to the methodologies applied and/or low quantity of studies that are able to respond to questions as: long-term exposure, discrepancy in the prevalence among men and women, evaluation of different routes of exposure and alternative methods to disinfection with chlorination
<i>Occurrence of disinfection by-products in swimming pools and the estimated resulting cytotoxicity</i>	Literature review	Carter et al., 2019	Pool waters analyzed contained a molar concentration until 100-fold higher of total DBP including THM in comparison with untreated filling waters. THM, HNM and HAA do not contribute significantly for the estimated chronic cytotoxicity
<i>National trends of bladder cancer and trihalomethanes in drinking water: a review and multicountry ecological study</i>	Systematic review of the literature	Cotruvo and Amato, 2019	The study did not find a strong or consistent connection between TTHM and bladder cancer. It supports the epidemiologic findings that the risk of bladder cancer by drinking water, if the case, is small and probably overweighed by many other greater risk factors
<i>Disinfection byproducts potentially responsible for the association between chlorinated drinking water and bladder cancer: a review</i>	Literature review	Diana et al., 2019	This study compared structures of DBP with 76 carcinogenic agents of bladder. Regulated THM and HAA are much less potent to explain the risk of bladder cancer than nitrosamines. In general, based in genotoxicity and cytotoxicity, nitrogenated DBP are more toxic than brominated which, on its turn, are more toxic than chlorinated

to be continued

Chart 1. continuation

Article	Method	Authors/year	Results
<i>Trihalomethanes: concentrations, cancer risks, and regulations</i>	Literature review	Cotruvo and Amato, 2019	Data of national tendency (USA) of bladder cancer since TTHM were found and regulated do not reflect a strong connection between TTHM and incidence of bladder cancer. The potential for measurable contribution of drinking water for cancer risk is not obvious and causality associated with drinking water was not determined
<i>The toxic potentials and focus of disinfection byproducts based on the human embryonic kidney (HEK293) cell model</i>	Experimental study in vitro	Chen et al., 2019	The tribromo acetaldehyde inhibits cells in very low concentrations. Regardless of not being an actual THM, this compound tends to transform in THM during its degradation. In general, regarding DBP metabolism, the target of the action of these byproducts was in the mitochondrial metabolism (production of ATP), lactic dehydrogenases and in the production of oxygen radioactive species
<i>Toxicological aspects of trihalomethanes: a systematic review</i>	Literature review	de Castro et al., 2019	It is necessary a broad understanding about the potential health risk, mainly because there are no experimental studies applied that most of the times do not reflect the reality of toxicology. A possible explanation for the differences in the toxicity of THM is that their compounds act in synergism or with toxicological additive effects among them. At last, another point to be considered is that most of the studies investigated in this review were in trials with bacteria, so it is possible that they do not have the same applicability in humans given the phylogenetic distance
<i>The unveiling of a new risk factor associated with bladder cancer in Lebanon</i>	Case-control study	Temraz et al., 2019	8.65% of bladder cancer was associated with the exposure to THM. This data do not reflect age, gender, location, socioeconomic factors, and life habits, which is a limitation. The necessity of a trustworthy study addressing the role of tobacco use and exposure to THM in synergy as risk factors for bladder cancer is highlighted
<i>Trihalomethanes in drinking water and bladder cancer burden in the European Union</i>	Case-control study	Evlampidou et al., 2020	The population-attributed fraction exposed to a mean concentration of 11.7 ug/L of THM in the water was 4.9%. Mathematically, this means 6,561 cases of bladder cancer affecting men and women annually older than 20 years of age
<i>Analysis of cumulative cancer risk associated with disinfection byproducts in United States drinking water</i>	Observational, longitudinal study based in monitoring dataset of unregulated US EPA (UCMR4) contaminants and data of occurrence of THM and HAA in more than 48 thousand communities. The dataset analysis addressed 4 regulated THM and 9 HAA. Risk levels based on data obtained were calculated	Evans et al., 2020	It is estimated that nearly 6,800 cases annually and 828 thousand cases during lifetime may have been caused by the presence of disinfection byproducts in drinking water in the USA. The cumulative risks based on epidemiological and toxicological studies are significantly greater than the US EPA's acceptable risk
<i>Contemporary issues on the occurrence and removal of disinfection byproducts in drinking water - a review</i>	Literature review	Chaukura et al., 2020	Notwithstanding the significant health risks, the knowledge of DBP adverse effects is still poor. Data on human risks are scarce and what is available is limited by the methodologies utilized to obtain toxicological data. Realistic environmental toxicological studies should be carried out to establish specific emerging DBP associated public health risks and produce extensive empirical data for future regulation of emerging DBP

Captions: GSTT1 = Glutathione S-transferase theta-1; OR = Odds-ratio; DNA = desoxyribonucleic acid; DBP = Disinfection byproducts; THM = Trihalomethanes; HAA = Haloacetic acids; TTHM = Total Trihalomethanes; GSTZ1 = Glutathione S-transferase zeta 1; CYP2E19 = Cytochrome P450 2E19; CYP2E1 = Cytochrome P450 2E1; ATP = Adenosine triphosphate; UCMR4 = The Fourth Unregulated Contaminant Monitoring Rule; USEPA = United States Environmental Protection Agency; USA = United States of America; Cl = Chlorine.

DISCUSSION

APPEARANCE OF TRIHALOMETHANES

The main precursor of THM is the molecule of methane where three atoms of hydrogen are replaced by three atoms of halogen. Halogens can be chlorine, bromate, iodine or its combinations – giving rise to four main subtypes of THM: chloroform, bromodichloromethane, dibromocholestane and bromoform¹⁴. A value known as total trihalomethanes (TTHM) is usually presented and is the sum of four individual THM more frequently encountered in treated water^{15,16}.

ROUTES OF EXPOSURE

The three main routes of human exposure to THM are oral intake, inhalation, and dermal contact. Human beings are exposed to THM mainly through direct ingestion of tap water, inhalation of volatile compounds and dermal absorption during bath and swimming in chlorinated pools^{12,17,18}. More specifically in pools, there is continuous addition of a wide range of disinfectants, natural chemical products, excretions of human bodies, pharmaceutical and toiletries products. Therefore, the total content of organic carbon is typically much greater than detected in drinking waters and the propensity of formation of THM is bigger^{15,19}.

REGULATION

In 1998, the regulatory level allowed for TTHM in USA went from 100 to 80 µg/L as an alternative measure to diminish the excessive risk of DBP-related cancer in drinking water as some epidemiological studies concluded, which mostly benefitted bladder cancer²⁰. After the issue of Ordinance number 36/1990²¹, the Ministry of Health determined that 100 µg/L is the upper limit of total THM in water allowed in Brazil.

THM AND BLADDER CANCER

Bladder cancer is the ninth most common cancer worldwide, has an annual incidence of approximately 430 thousand cases and is ranked 13 in annual mortality by cancer²². The incidence of bladder cancer is strongly related to age. Nearly 90% of bladder cancer occur in individuals over 55 years of age. In addition, men has from two to four more odds of developing bladder cancer than women during the lifetime². One of the hypothesis is the role that androgens and estrogens with different physiologic effects that can differ among genders have in the carcinogenic process²³. Specifically in Caucasian males, this probability doubles when compared with African-descendant men.

Overall, epidemiology tends to vary according to the country as many cultural habits can be considered risk factors for this disease, mainly tobacco use²³. Other conclusive risk factors are the exposure to aromatic amines and polycyclic hydrocarbons, type 2 *diabetes mellitus*, ethnicity, kidney transplantation, overweight, obesity, human papilloma virus (HPV), HIV-infections, occupational exposure to arsenic among others². Genetic susceptibility also contributes as an important risk factor. The most solid evidence found is glutathione S-transferase Mu 1 null polymorphism (GSTM1)²³. As for the exposure to DBPs, specially to THM, the evidence that establish the main mechanism of action involved in the process of carcinogenesis of bladder cancer remains uncertain²³.

In 1991, the International Agency for Research on Cancer (IARC) classified the THM in general as carcinogenic of the group 3 and group 2B. There were not enough evidence proving the relation between the exposure to THM and increase of mortality because of bladder cancer and of other neoplasms in humans²⁴ most of all because of methodological limitations the studies presented²⁵. Among them, the difficulty of quantifying the influence other risk factors as air pollution, lifestyle, nutrition, and occupation jointly with THM in the carcinogenic processes²⁵. Regardless of this, new studies discuss a possible change in this scenario, especially one of them conducted through systematic meta-analysis which demonstrates the role of THM as preponderant risk factor in the development of bladder cancer – predominantly in males²⁶.

It is known that the subclass of THM appear to be related with a different action mechanism, therefore, the effects can be genotoxic, mutagenic and/or cytotoxic¹. A review published ten years after the IARC classification evaluated the toxicologic effects of chloroform and demonstrated there were no mutagenic properties^{27,28}. It means that at least this subclass of THM changes the cellular integrity and can cause damages not successively and insufficient to the point of modifying the sequence of DNA nucleotides^{8,29}. When evaluated in assays utilizing bacteria and eucaryotic cells of rodents, it presented as chemical agents with cytotoxic potential, involving processes of cellular death and inactivation while interfering in the cytochrome P450 2E1 (CYP2E1)^{1,8}. During this reaction, phosgene is generated as an intermediate able to react with phospholipids, bind to proteins and reduce the activity of glutathione⁸. It was demonstrated in a study that exposure to DBP when associated with polymorphisms of CYP2E1 increased the risk of development of bladder cancer⁸.

A USA study indicated that adult individuals with high levels of brominated THM in the blood – bromoform

(1.2pg/mL), bromodichloromethane (4.1pg/mL) – have 4-fold more risk of developing cancer^{30,31}. In relation to brominated THM, the mechanism of action is mutagenic and is connected to the disorder of the system of glutathione-S-transferase, more specifically Theta 1 (GSTT1-1). As the metabolization process is damaged, THM carbonyl reactive molecules are generated with potential of binding to DNA in *in vitro* assays⁸. Regardless of glutathione being also related to the mechanism of action of cytotoxicity of the chloroform, brominated THM has the potential of changing the metabolism of these enzymes through conjugation of the gene GSTT1-1 at lower doses³¹. An experimental study in *Salmonella sp* bacteria in assays of DNA mutation evaluated the level of mutagenicity and cytotoxicity of brominated THM through the analysis of the gene of GSTT1-1 with less expression. In this experiment, it was concluded that bromoform and dibromochloromethane presented greater mutagenic and cytotoxic risk if compared with bromodichloromethane³¹.

There are individuals more predisposed to undergoing alterations in the action of glutathione as they have genetic polymorphisms acting together just in the formation of these enzymes. A Spanish study demonstrated that the association between the exposure to THM and bladder cancer was stronger in individuals with polymorphisms in the genes GSTT1 and GSTZ1 which codify the enzymes glutathione-S-transferase, responsible for the metabolization of brominated THM. By this mechanism, brominated THM would have the ability of scaping the hepatic metabolism of first passage and reach the target-tissue in the urinary tract being activated in intermediary mutagenic^{30,32}.

Most of the studies identifying the mechanisms of action of the THM involved in the carcinogenic processes of bladder cancer were developed in assays with bacteria and fungi – where the mechanisms are mutagenic and cytotoxic through the applicability of assays evaluating the deletion recombinant *in vitro* utilizing *Saccharomyces RS112* and the evaluation of the mitochondrial DNA in *Salmonella*. Consequently, it may not have the same applicability in humans given the phylogenetic distance¹. For better evaluation of the toxicologic effects of the THM related to bladder cancer in humans, other parameters were utilized in epidemiologic studies³³.

Beane Freeman et al.²⁷ demonstrated increase of the odds of development of bladder cancer in populations exposed to a mean concentration of THM above 45 µg/L. Data of six case-control studies, for instance, showed that the group exposed to these concentrations resulted in odds ratio of 1.4 (95%CI, 1.2-1.7) for the development of the disease^{8,34}.

Toxicity also varies according to the routes of exposure. Ashley et al.³⁵, Leavens et al.³⁶ and Lewis et al.³⁷ (apud Villanueva⁸) concluded that the internal dose and time of excretion of THM in the blood flow were greater in cases where this substance was inhaled or absorbed by dermal route. Nevertheless, in despite of these routes presented lower metabolism, another study of Beane Freeman et al.²⁷ demonstrated that the odds ratio for the development of bladder cancer were greater in the routes of exposure of cumulative intake (1.45) and in mean daily intake (1.53).

The United States Environmental Protection Agency (USEPA) affirmed that bladder cancer risks reported in epidemiologic studies can be inexistent because of non-causality yet established. These THM-targeted studies and its relation with bladder cancer are limited because the latency periods for bladder cancer are unknown since there is no consensus about the time of development after initial exposure. Nevertheless, it is estimated that in average, it ranges from ten to 30 years or more^{2,38}. In addition, the potential risks are probably overburdened by other risk factors in humans like tobacco use, gender, race, age, and other comorbidities. Most of the epidemiologic studies analyzed only one variable – this is particularly limiting given the complexity of the etiology of bladder cancer^{2,34,39}.

Therefore, the measurable contribution of exposure to THM in drinking water for carcinogenic risk is unclear^{2,34,35}. In addition, another key aspect to ponder is that the contribution of THM to the water in the long-term can vary depending on temperature and/or pH resulting in different contributors and/or routes of exposure that may have gone unaddressed in the studies^{2,34}.

For nearly 40 years, TTHM are regulated and are the most prevalent disinfection byproduct and because of this the measurement of the total concentrations is utilized in some studies as a representative parameter to evaluate the concentration of DBP as a whole²⁷. The implication of this quantification is that the influence of other DBP, generated during the chlorination process, including the unregulated and/or undefined, can have in the toxicological processes remains obscure. According to the literature, the unregulated byproducts and less reported can present genotoxicity and cytotoxicity bigger in human beings²⁶. The assumptions that TTHM are the only responsible for carcinogenicity is challenged since its toxicologic effects can be the result of the synergism with other potentially carcinogenic DBP^{2,34,40}.

Although the potential risks of bladder cancer associated with the presence of THM in drinking water remain questionable, proper practices and strategies should be pondered to keep the quality of the drinking water to avoid undesired excessive exposures^{2,34}. The use of alternative disinfectants as ozone, chlorine dioxide

and chloramines is already been investigated because it is known that the application of these disinfectants reduces the concentration of the four regulated THM⁴¹. However, the use of these disinfectants as strategy to diminish the risk is still debatable as they could form a new set of unregulated DBP and with more toxicity³⁸. Unavoidably, whenever a disinfection method is applied, its reaction generates byproduct, and it is necessary to evaluate the risk *versus* benefit they have⁸. Thus, it is paramount to add toxic emerging DBP to the standards of quality of water which can contribute to reach the goal of making drinking water safer³⁸. The removal of precursor DBP as natural organic matter is also a strategy that has been effective. Methods as coagulation, advanced oxidation and ultrafiltration by membrane are the most common, however, more effective, and economic methods are necessary³⁸.

CONCLUSION

Bladder cancer carcinogenic processes occur, most of all, as a consequence of genetic, epigenetic and exposure factors as reported in the current literature review, which hampers the determination of one risk factor alone as preponderant for its development.

Despite the significant health risks, bladder cancer THM related impacts remain questionable. Data on human risks are scarce and what is available is limited by the methodologies utilized to obtain epidemiologic data. It is not possible to confirm whether this association is causal because THM and most of other identified DBP continue with unknown biologic activities. It is acknowledged, therefore, that many studies should still be targeted to confirm this relation.

CONTRIBUTIONS

Beatriz de Almeida Affornalli, Nadinne Maria Macetti and Camila Moraes Marques contributed substantially for the study design/conception, collection, analysis and/or interpretation of the data, wording, and critical review. Diancarlos Pereira de Andrade and Rosiane Guetter Mello contributed for the analysis and/or interpretation of the data, wording, and critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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