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REVIEW ARTICLE

Challenges of disinfection by-products in water and effect on the men's health infertility- A Narrative review

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Abstract: Chlorination is the most common disinfectant in the water treatment process. The reaction between Natural Organic Matter (NOM) in water and chlorine lead to the formation of harmful disinfectant by-products (DBPs). The most common DBPs (HAAs and THMs) impose risks on human health. The data acquired from human samples on the relationship of men's infertility with DBPs exposure are limited and epidemiological studies have reported various results about the association between long-term exposure to DBPs and the adverse effect on the man's infertility (sperm concentration, semen quality and sperm motility). Previous cellular studies show that HAAs and THM damaged DNA by their effect on the ROS generation and Oxidative stress, respectively. Moreover, CDBM can lead to decreased litter sizes and pup viability. Bromodichloromethane (BDCM) cause the production of sperm abnormalities. In addition, Trichloromethane (TCM) led to increase the degeneration of epididymis ductal epithelium. Dibromoacetic acid (DBAA) and Bromochloroacetic acid (BCAA) led to synergistical decrease in the levels of SP22 sperm membrane protein. Likewise, BCAA and DBAA resulted in testicular damage. It should be noted that synergistic effect between Br THMs and TCAA in relation to below-reference sperm count was demonstrated. It has been reported that mixture of THMs and HAAs lead to increase sperm motility in adult male rats.

Keywords: Drinking Water; Disinfection; Reproductive health; Infertility; Male

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1. Introduction

Over the past decade, access to safe drinking water has become a challenge. Disinfection of the drinking water available to the public is one of the most important stages in the water treatment process, and is aimed to protect the population against waterborne infection diseases [1, 2]. Toxicological studies have reported adverse effects that long-term exposure of organic contaminants in water can have on human health [2]. Disinfection by-products (DBPs) are the group of environmental chemicals which form by the reaction of organic matter and chlorine as a disinfectant in raw water [3]. To date, different categories of DBPs have been identified. Trihalomethanes (THMs) and Haloacetic acids (HAAs), amongst all DBPs, have exposed potential risks on human health. These concerns include the potential for cancers as well as adverse pregnancy outcomes in the general population [4]. Humans can be exposed to DBPs through various ways, such as ingestion, inhalation, and dermal absorption during drinking, bathing, showering, and swimming [5]. In the recent decades, epidemiological studies have reported a decline in semen quality, and the effects of environmental factors such as exposure to chemical pollutants is undeniable [6-9]. Much concern has been raised regarding the reproductive health consequences of exposure to persistent DBPs in water consumption. Here, this narrative review study summarizes the current evidence on DBPs with regard to occur-

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rence, animal experimental results, effect on men's health, and other varying effects of exposure to DBPs on semen quality and infertility, and will conclude by suggestions for directions in future research.

2. Occurrence and Regulations

Chlorine as a disinfectant is commonly used for water disinfection worldwide, and the reaction between organic matter in the water and chlorine lead to formation of DBPs in water. Richardson reported that more than 600 DBP compounds have formed by the reaction of organic precursor (natural organic matter, algal organic matter, wastewater effluent organic matter) and inorganic substance, (bromate, iodate and nitrate) as well as in reaction with chemical disinfectants (chlorine, chlorine dioxide, chloramines and ozone) (Fig.1). Moreover, formation of DBPs depends on several factors, such as disinfectant concentration, contact time, pH, temperature, and NOM concentration [10]. Therefore, United States Environmental Protection Agency (USEPA) and World Health Organization (WHO) have recommended varying threshold maximum contaminant level (MCL) for DBPs in water (Table.1). Water quality standard for Iranian drinking water is also summarized in Table.1

3. Health risk

Previously, several epidemiologic studies reported an association between the exposure of DBPs in water and varying health effects on animals, such as adverse male reproductive effects, including reduced reproductive organ weights, impaired reproductive competence, and decreased semen quality [13-16]. Moreover, some epidemiological studies reported the exposure of DBPs in drinking water and varying effects on human health such as the risk of different types of cancer [17, 18], adverse pregnancy outcomes [19-24], spontaneous abortion, birth defects, [25, 26] genotoxic and mutagenic potential, [27-31] and male semen quality [32, 33]. In addition, DBPs are activated to mutagenic intermediates by metabolic enzymes and subsequently cause oxidative stress, which has been suggested as the potential mechanism of their male reproductive toxicity [34]. However, only a few studies are available and therefore more knowledge is required [35, 36]. Therefore, DBPs have become a public health concern. Overall, the association between DBPs and health effects in various countries have shown to be relatively consistent. However, there is debatable bias in different reports due to inconsistencies in the several effective factors such as age, gender, smoking statue, origin of water sources, and dose of chlorination.

3.1. Cellular effects

It has been widely documented that the DBPs have adverse impacts on public health and influence different tissues such as the liver, kidney, nervous system, and reproductive system[37]. The mutagenic, genotoxic, and cytotoxic, as well as teratogenic activities of HAAs have been recognized [38]. The mono-HAAs including iodo-acetic acid (IAA), bromoacetic acid (BAA), and chloroacetic acid (CAA) were studied in terms of their toxicity level and it was indicated that IAA is more toxic compared to BAA and CAA [39]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is an important enzyme for glucose metabolism to pyruvate and the electron transport chain. Inhibition of this enzyme can disrupt the chain and result in the generation of reactive oxygen species (ROS)[40]. Therefore, mono-HAAs such as IAA induce cell damage and death via inhibiting this glycolytic enzyme and ROS production, particularly in vital organs such as the brain. In fact, alkylating potential of mono-HAAs corresponds to the inhibition of GAPDH [30]. ATP depletion leads to water and/or fat accumulation in epithelial cells (hydropic degeneration) and hepatocytes (fat liver or hepatic steatosis), and cause irreversible cellular damage in severe and chronic cases [41]. Overall, mono-HAAs can induce Geno toxicity and damage to genomic DNA and resultant cellular necrosis by ROS generation.

Accordingly, use of antioxidants such as catalase decreases the HAA-induced cytotoxicity and Geno toxicity and consequently interfere the free radicals [40]. On the other hand, a concentration-dependent reduction in the level of cellular ATP and suppression of pyruvate production with GAPDH inhibition has been found. Reduced amounts of pyruvate can lead to mitochondrial stress and resultant genomic DNA damage. Based on this, supplementation of pyruvate could increase cellular ATP levels and eliminate genomic DNA damage and Geno toxicity induced by mono-HAAs [40]. Given the action mechanisms related to neurotoxic potencies of DBPs, GADPH inhibition and subsequent generation of ROS may play a substantial role in neurodegenerative diseases, such as Alzheimer's disease. In addition to neurotoxic, genotoxic, teratogenic, and mutagenic potencies of HAAs through GAPDH inhibition and free radicals, they can also be carcinogenic [42, 43]. Regarding the carcinogenic potency of HAAs in the liver and kidney of mice, it has been indicated that DCAA and trichloroacetic acid (TCAA) are capable of inducing cell proliferation. Increased mRNA levels of some proto-oncogenes, such as c-myc that were involved in cell proliferation and apoptosis, have been noticed in mouse liver tumors treated with DCAA and TCAA. 5-methylcytosine in DNA controls the mRNA transcription of c-myc. TCAA and DCAA can diminish methylation of these proto-oncogenes and thus enhance their mRNA levels [44]. DBPs can also ex-

Table 1: Regulatory DBP limits and health guidelines (mg/L) for drinking water[12]

DBPs Species	DBPs	Drinking Water Standard (mg/L)			Carcinogenicity
		USEPA	WHO	Iran	
THMs (Human carcinogen)	Chloroform ($CHCl_3$)	0.02	0.02	0.03	B_2
	Bromodichloromethane ($CHCl_2Br$)	0.08	0.06	0.06	B_2
	Dibromochloromethane ($CHClBr_2$)	0.08	0.1	0.1	C
	Bromoform ($CHBr_3$)	0.08	0.1	0.1	B_2
HAAs	Dichloroacetic acid (DCAA)	0.06	0.05	0.05	B_2
	Trichloroacetic acid (TCAA)	0.06	0.2	0.2	B_2

USEPA (2012); B_2: Sufficient evidence from animal studies); Group C: Possible human carcinogen.

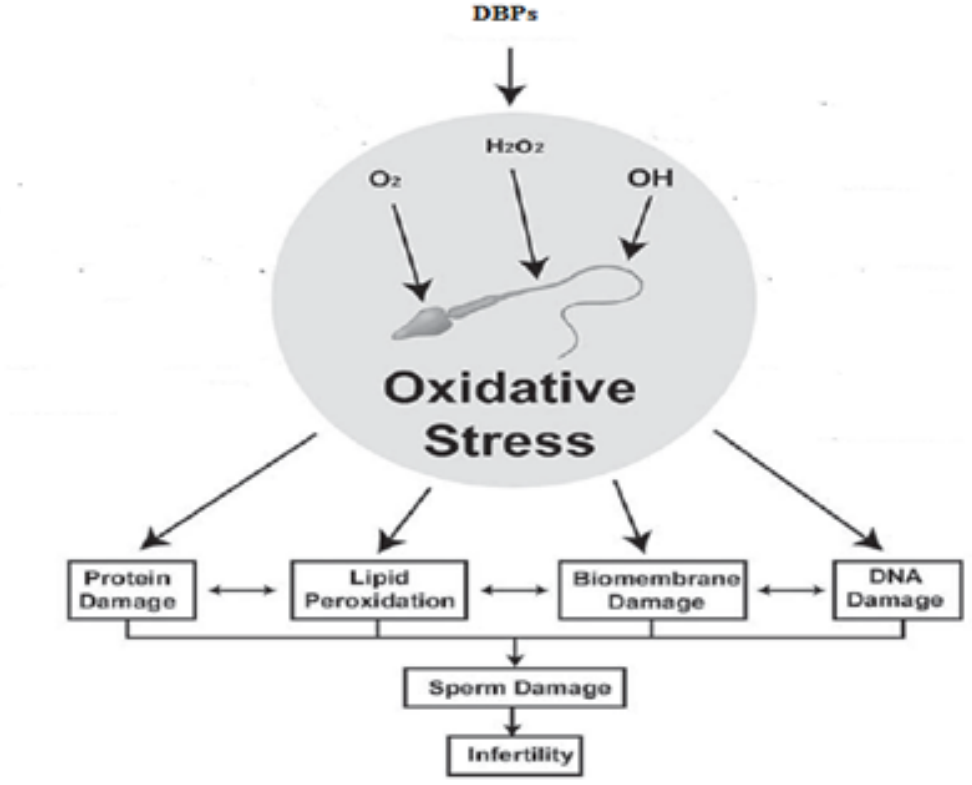

Figure 1: Association of increasing reactive oxygen species (ROS) production with infertility[49].

ert the deleterious effects on reproductive system and cause developmental abnormalities. They can cause a reduction in body weight and survival of the offspring, in addition to developmental toxicity and abortion. Likewise, it has been reported that parental exposure to DBPs, such as THMs and dichloroacetic acid (DCAA), increased the risk of stillborn in Massachusetts, USA [4]. It has been found that HAAs can disrupt spermatogenesis and therefore cause testicular damage [45]. THMs, including chloroform, bromoform, bromodichloromethane (BDCM), and dibromochloromethane (DBCM), are one of the most common DBMs of chlorinated water [46]. Colorectal and urinary bladder cancers associated with bathing and swimming have been reported with long-term exposure to THMs. It has been indicated that the order of Geno toxicity and DNA-damaging potential of HTMs is at follows: BDCM > DBCM > bromoform > chloroform [47]. Oxidative stress seems to play a crucial role in THM-mediated DNA and cellular injury. In addition, THMs may interfere with energy metabolism, reduce ATP production, and cause cellular ROS generation and accumulation (Figure.1 and 2)[48].

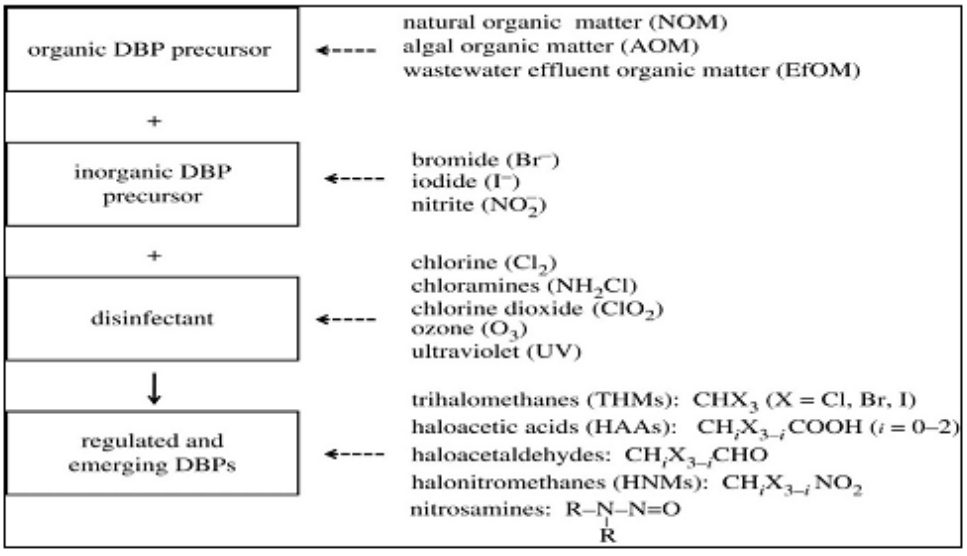

Figure 2: Schematic diagram of the reaction of organic and inorganic DBP precursors with disinfectants to form regulated and emerging DBPs[11].

Table 2: Reproductive Outcomes

Outcome	Type of DBPs	Ref
Percent sperm motility	HAA(TCAA)	[62]
Decrease in serum testosterone concentration	THM	[63]
Decrease in percentages of progressively motile sperm and progressive tracks and decrease in sperm membrane proteins	HAA(BCA)	[64]
Decreases in the fertility of cauda epididymal sperm	HAAs (DBA)	[65]
Decreased sperm count, decreased sperm, decreased serum total testosterone	∑ THMs	[66]
Decrease in sperm concentration, sperm count, sperm morphology and sperm motility	HAA(TCAA)	[62]
Spermiogenesis disruption, decrease in sperm protein	HAA (DBA)	[67]
sperm abnormalities, decreased sperm motility	THM (BDCM)	[68]
Decreased litter sizes and pup viability	THM (CDBM)	[69]
Sperm concentration, sperm motility	HAA(TCAA)	[70]
Sperm count, total motility and progressive motility	TTHMs (TCM, DBCM, Br-THMs)	[71]
Decrease in spermatocytes and spermatids, as well as on the cytoplasmic droplet and the equatorial segment of luminal sperm	HAA (DBA + BCA mixture)	[72]
Adverse sperm effects, changes in male, reproductive organs.	HAA (DBAA)	[73]

3.2. Disinfection byproducts and Reproductive Outcomes

Several studies evaluated the effects of halogenated byproducts on adverse reproductive outcomes, and some studies have developed to investigate toxicity in laboratory animals. However, oral administration of various classes of THM has reported different results. Chloroform showed little reproductive effect, growth retardation, and pregnancy loss. Bromoform and BDCM showed no effect on reproductive indices. Klinefelter et al. has demonstrated that BDCM produces sperm abnormalities in male rats as indicated by decreased sperm motility. Other lectures have reported that CDBM can lead to decreased litter sizes and pup viability in laboratory rats. However, Ruddick et al. found no evidence for fetotoxic or teratogenic effects at lower doses. Reproductive effects of halogenated acetic acids have also been investigated by previous lectures and have shown testicular damage in rats. Moreover, based on in vitro studies, it has been found that brominated analogue is the stronger toxicant. In addition, neural tube defects is one of the most important stud-

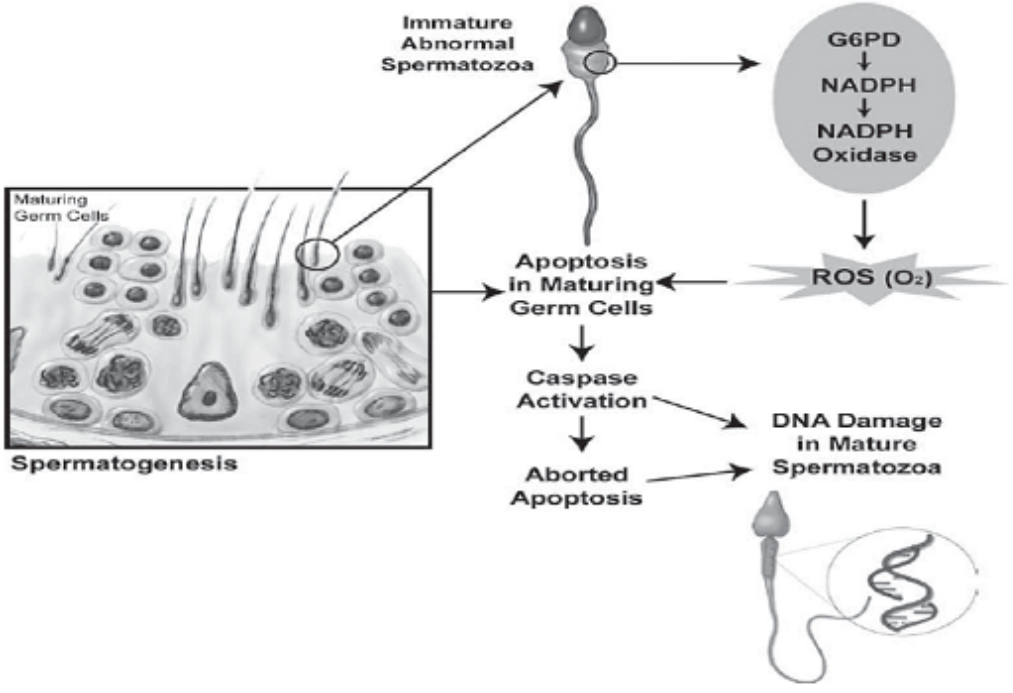

Figure 3: Mechanistic pathway showing sperm DNA damage due to oxidative stress[49].

ies on laboratory animals, and exposure with HAA showed changes in neural tube development in mouse embryos [50], and the results presented in lectures are different. Some studies reported statistically significant positive association between THM levels in water and neural tube defects in animals [19, 51, 52]. Whereas, other studies did not find any positive association [53-56]. In addition, increased body fat, increased malformations in the cardiovascular, digestive, and genital systems, malformation of soft tissue, and ovarian toxicity are reported by previous studies [57-59]. However, toxicological effects of the many other DBPs have remained unknown. Several epidemiological studies have been carried out to investigate the association between DBPs in drinking water and reproductive outcomes (Table 2). Fenster et al. suggested a possible association of ingested total THMs with a decrease in normal sperm morphology [60], whereas Luben et al. reported a decrease in sperm concentration with increasing exposure to total organic halides, a global measure of halogen-containing DBPs [61]. However, another study has reported that exposure to mainly HAAs (another important class of DBPs) are associated with poor semen quality in animals [32].

3.3. Fertility

Potential effect of DBP compounds on male fertility has not attracted much attention. However, there is some animal-based evidence. To the best of the authors' knowledge, there are small epidemiological studies based on various population groups. However, studies have reported negative effect of DBPs on sperm morphology and concentration, but the evidence is not clearly found in the effect of DBPs on sperm motility percentage. In reality, DBPs exist as complex mixtures in drinking water. Therefore, limited studies exist to evaluate reproductive toxicity of THMs and HAAs on the human and animals separately. However, there is no comprehensive information on DBPs' effect on human that have reported combined reproductive toxicity of any mixtures of DBPs compounds, while there is some studied in adult rats. Narotsky et al. found that exposure of adult male rats to mixture concentrate of DBPs, reduce sperm count that indicating a potential additive effect on adverse male reproductive health [74]. Another study demonstrated an association between HAAs and adverse effects in male reproductive system of animals [75]. Even so, toxicology study on humans suggested that brominated species of HAAs could pose a risk to male reproductive system [40]. According to previous exper-

imental study, exposure to TCM via gavage lead to increase the degeneration of epididymis ductal epithelium in the generation male mice [76]. From this point of view, Kaydos et al. reported that exposure of rats with mixtures of DBAA and BCAA lead to synergistical decrease in levels of SP22, a sperm membrane protein that is highly correlated with male fertility [72]. In laboratory animals, daily exposure to BCAA and DBAA resulted in testicular damage in rats [73]. In another study, result shows that DBAA appears to be a stronger testicular toxicant than BCAA [77].

3.4. Semen quality

Several studies have been carried out on whether exposure to DBPs contributes to declining semen quality [78-80]. The effect of DBPs; on the other hand, is variable based on different patterns in personal consumption of tap water, showering and other consumption routes.

Other toxicology studies suggest that brominated HAAs could pose a risk to outcomes in human semen such as sperm numbers, morphology, and motility. Thomas et al. reported no correlation between exposure to HAA and THM that shows decrease in sperm concentration. In addition, a smaller proportion of abnormal outcomes with increasing DBP exposure were reported [61]. Whereas, previous toxicology studies presented changes in sperm morphology at the lowest DBP doses, at higher doses adversely effect on the sperm morphology, sperm motility and epididymis sperm counts were observed [61]. From a different point of view, Fenster et al. suggested a possible association of ingested total THMs with decrease in normal sperm morphology also, HAAs associated with poor semen quality in animals was determined [60]. It should be noted that synergistic effect between Br THMs and TCAA in relation to below-reference sperm count was demonstrated [33, 81]. Moreover, a synergistic effect between exposure Br-THMs and TCAA and below sperm count was observed [82]. Documented results showed that relation between TCM and TTHM with decreased sperm concentration [34] while two previous studies reported no association between TTHM and semen quality [60, 61]. However, effect of DBPs dosage is not deniable and it has been suggested that higher levels of TTHM have an adverse effect on the percent normal sperm morphology [61]. These findings suggest that there is an inverse association between sperm concentration and total organic halides (TOX)[70]. Narotsky et al. reported that mixture of THMs and HAAs lead to increased sperm motility in adult male rats [74]. Whereas, Zengno et al, find no apparent joint effects between THMs and TCAA for sperm motility [82]. Previous lecturers suggested that exposure to THMs damage the testes resulting in decreased semen quality and serum total testosterone [83, 84].

4. Conclusion

It has been proved that long-term exposure of DBPs in water have adverse health effects on human health, such as increased risk of cancer, adverse pregnancy outcomes, and genotoxic as well as mutagenic potential. Several studies have documented the association between DBPs and pregnancy outcomes. However, the evidence shows a gap in the evaluation of men's health fertility by using narrative review. Lectures have documented different results of association between DBPs and reproductive outcomes. This narrative review summarized that HAAs and THM damaged DNA by effecting the ROS generation and Oxidative stress, respectively. Moreover, CDBM leads to decreased litter sizes and pup viability. BDCM causes the production of sperm abnormalities. In addition, TCM leads to increased degeneration of epididymis ductal epithelium. DBAA and BCAA lead to synergistical decrease in the levels of SP22, a sperm membrane protein. Likewise, BCAA and DBAA resulted in testicular damage. It should be noted that synergistic effect between Br THMs and TCAA in relation to below-reference sperm count was demonstrated. And lastly, it has been reported that mixture of THMs and HAAs lead to increase sperm motility in adult male rats.

5. Appendix

5.1. Acknowledgements

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5.2. Authors Contributions

All the authors have shared the same workload and thereby are entitled to equal acknowledgement.

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5.4. Conflict of Interest

The authors declare that there is no conflict of interest in the publication of this paper.

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