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Formation and Health Effects of Disinfectants and Disinfection by Products in Water Treatment: A Review

Benti Firdissa

Abstract
The objective of the review was to assess the impacts of disinfectants and disinfection by products on human heal and animals. Disinfection of drinking water was introduced to ensure that our water supply was microbiologically safe through the removal of pathogens. Although disinfectants are used to safe water, they cause DBPs by reacting with organic matters and inorganic once. Those DBPs cause important impact on human health. For instance cancer, impact on reproduction, respiration and allergy are the most well-known studies conducted. Bladder cancer is the most studied and much of studies reported positive association between bladder cancer and DBPs. However, others reported negative association between pancreatic cancer and DBPs. mixed result was obtained from studies conducted regarding respiratory and allergy. Studies from Belgium investigated positive association between DBPs and respiratory problems whereas others don't. In the case of reproduction and development, more studies reported the association of disinfectants and birth outcome whereas others don't this may be due to usage of different methodologies in disinfecting water. However animal study shows consistency on the impact of disinfection byproducts regarding reproductive system.
Keywords: Cancer, DBPs, Disinfection, Disinfectants, Water treatment

INTRODUCTION

Water resources and it's maintain of quality are important issues in human life. Disinfection of drinking water was introduced to ensure that our water supply was microbiologically safe through the removal of pathogens to prevent waterborne disease transmission because of the fact that many human diseases are related to water-borne pathogens, mainly if the drinking water is affected by wastewater or human or animal excretions. Diseases arising from the ingestion of pathogens in contaminated water have the greatest health impact worldwide. The health effects of these diseases are heavily concentrated in the developing world and, within the developing world, among the poorer urban and rural households of the poorer countries (Hend Galal-Gorchev, 1996).

An estimated 80% of all diseases and over one-third of deaths in developing countries are caused by the consumption of contaminated water and, on average, as much as one-tenth of each person's productive time is sacrificed to water-related diseases (UNCED, 1992). Typhoid and Cholera are among the diseases caused due to untreated water. To get quality water, people have disinfected drinking water since the end of the 19th century (Zwiener and Richardson, 2005). Before disinfectants were used widespread, huge numbers of humans died of cholera, typhoid and other waterborne diseases (Stefan, 2007).

Drinking water disinfection

Disinfection is a process used in drinking water treatment to inactivate pathogenic microorganisms. Depending on its application within the system, disinfection is classified as either primary or secondary disinfection. Primary disinfection is aimed at inactivation of microorganisms and is done at the water treatment plant. Secondary disinfection is aimed at protecting water in the distribution system from microbiological regrowth and contamination (Maruf and Syed, 2006).

Different water disinfectants and processes are used in the world. Chlorine, ozone, chloramine and chlorine dioxine are the most used disinfectants to minimize the number of the pathogens in water. Chlorine has been the most important disinfectant for drinking water for many decades (Reif, *et al*., 1996). Chlorine, ozone, chlorine dioxide, and chloramines are the most common disinfectants in use today, and each produces its own suite of chemical DBPs in drinking water (Richardson, 2005).

Formation of DBPs

Disinfection by-products (DBPs) consist of a wide variety of chemicals that form when chlorine is added to drinking water during the treatment process. Chlorine is added to drinking water for disinfection purposes. Disinfection byproducts and deterioration of the distribution system pipe network are among the primary concerns for disinfection process (Maruf and Syed, 2006).

DBPs are formed when disinfectants reacts with the natural, organic materials found in water, such as algae and decaying plants. The formation of byproducts is dependent on the chemical composition of the water and the disinfectant used during the treatment process (Maruf and Syed, 2006). In addition pH, temperature and contact time influence the formation of byproducts. The two reactants (chlorine and organic content) are present in the drinking water throughout its transit to the consumers tap. Therefore, the reactions leading to the formation of DBPs are present throughout the distribution system (Maruf and Syed, 2006).

The first DBPs—chloroform and other trihalomethanes (THMs)—were identified and reported by Rook in 1974 in chlorinated drinking water (Rook, 1974). Since then studies focus on DBPs and describes approximately 600-700 DBPs today which are formed by the common disinfectants (Krasener, *et al*., 2006) with THMs and HAAs accounting for more than 80% of the total amount (Leu, *et al.,* 2011).

Chlorination and by products

It is a process using chlorine to destroy pathogenic bacteria and algae in raw water.

Chlorination is the process of adding chlorine (Cl_2) into water: $Cl_2 + H_2O \rightarrow HOCl + HCl$. Conditions for effective terminal chlorination as recommended in the WHO Guidelines for drinking water quality are as follows (WHO, 1996; Clark *et al.,* 1993):

pH less than	8.0
Median turbidity	not to exceed 1 nephelometric turbidity unit (NTU)
Maximum turbidity	5 NTU
Residual concentration not less than	0.5 mg/L
Contact time at least	30 min

This reaction takes place in the first few seconds. The magnitude of the equilibrium hydrolysis constant is such that hydrolysis to hypochlorous acid, HOCl, is virtually complete in fresh water at pH > 4 and at chlorine doses up to 100 mg/liter (Morris, 1982). Hypochlorous acid is a weak acid that dissociates partially in water as follows: HOCl = H+ + OCl-

Chlorination has played a critical role in protecting drinking water supplies from waterborne infectious diseases for 90 years. One of the earliest uses of chlorine as a disinfectant was introduced by Dr. Ignaz Semmelweis in 1846 (Keith, 1996). One of the first known uses of chlorine for water disinfection occurred in 1854 (Keith, 1996). Chlorine revolutionized water purification, reduced the incidence of waterborne diseases across the western world, and "chlorination and/or filtration of drinking water has been hailed as **the** major public health achievement of the 20th century" (Calderon, 2000) and it is still the most widely used disinfectant due to its low cost, easy acquisition and persistent effect (Golfinopoulos and Nikolaou, 2005). As the level of chlorination is increased the risk continues to drop slightly, but never quite reaches zero, for no system is perfect (Morris, 1978) (Figure1).

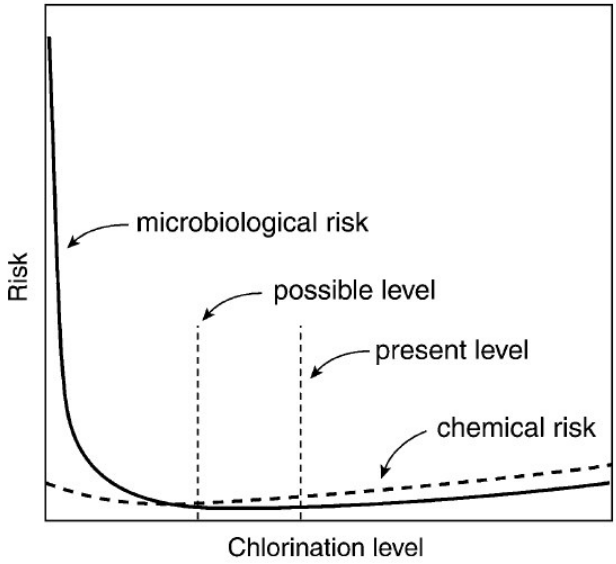


Fig. 1: Risks and benefits of water chlorination Source: Morris (1978**)**

DBPs are formed when chlorine reacts with the natural, organic materials found in water, such as algae and decaying plants. Chlorine + Organic matter=DBPs. Chlorine disinfectants these molecules and break them down into simpler assailable molecules (Ahmed and Saad, 2005). More than 300 reported DBPs are formed from chlorination (Stefan, 2007). The two major classes of formed DBPs are trihalomethanes (THMs) and haloacetic acids (HAAs). In addition to this halogenated acetonitriles, chloral hydrate and the chlorinated phenols are formed. Others include chlorinated furanone MX, halopicrins, cyanogen halides, haloketones and haloaldehydes. The first two classes of these compounds are the ones that are currently receiving most concern and attention (Ahmed and Saad, 2005).

Trihalomethanes

The predominant chlorine disinfection by-products are the THMs. Nevertheless, they account for only about

10% of the total organic halogen compounds formed by water chlorination. THMs are formed by the aqueous chlorination of humic substances, of soluble compounds secreted from algae and of naturally occurring nitrogenous compounds (Morris, 1982). Another factor is the contact time between raw water and chlorine. At the center of each of the four trihalomethanes is a carbon atom, and it is surrounded by and bound to four atoms: one hydrogen and three halogens. These four compounds are collectively termed trihalomethanes and are abbreviated as either THM or TTHM (for total trihalomethanes).

Potent trihalomethanes (THMs) of four species can be formed as disinfection by-products in chlorination (Rook, 1974; Bellar, *et al*., 1974). They are Chloroform ($CHCl_3$), Bromodichloromethane ($CHBrCl_2$), Dibromochloromethane ($CHBr_2Cl$) and Bromoform ($CHBr_3$). Since then THMs have been researched intensively (Mok, *et al.,* 2005) with Lifetime cancer risk of 1/100000 at a concentration of 1.9 µg/l.

The origin of chloroform can be illustrated by the interaction between chlorine and propanone. Propanone (an example for organic matter) will be oxidized into trichloropropanone if water became chlorinated (Stefan, 2007).

$CH_3COCH_3 + HOCl \_ CH_3COCCl_3$

In the following reaction, trichloropropanone becomes hydrolyzed, especially at high pH:

$CH_3COCCl_3 + H_2O \_ CH_3COOH + CHCl_3$

When bromide is present in drinking-water, it is oxidized to hypobromous acid by chlorine:

$HOCl + Br^- = HOBr + Cl^-$

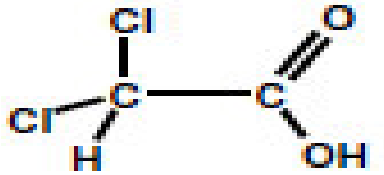
HOBr reacts with natural organic compounds to form brominated halomethanes. Similarly, the presence of iodide may lead to the formation of mixed chlorobromoiodo methanes. Brominated and iodinated DBPs form due to the reaction of the disinfectant (such as chlorine) with natural bromide or iodide present in source waters (Richardson, 2005). Coastal cities, whose ground waters and surface waters can be impacted by salt water intrusion, and some inland locations, whose surface waters can be impacted by natural salt deposits from ancient seas or oil-field brines, are examples of locations that can have high bromide and iodide levels (Richardson, 2005).

WHO (2004) proposes the use of an additive toxicity guideline value, using the fractionation equation that the sum of the four THMs' actual concentration (C) divided by their guideline value (GV) should not be greater than

$$\frac{C_{Chloroform}}{GV_{Chloroform}} + \frac{C_{BDCM}}{GV_{BDCM}} + \frac{C_{DBCM}}{GV_{DBCM}} + \frac{C_{Bromoform}}{GV_{Bromoform}} \leq 1$$

Using of alternative disinfection methods (ozone, chlorine dioxide, and chloramines) minimized the formation of the four regulated THMs however other priorities DBPs were formed at significant concentrations (Richardson, 2005). For example, iodo-THMs were highest at a plant using chloramines only (up to 15 ppb, individually); dihaloaldehydes were highest at a plant using chloramines and ozone (up to 16 ppb, individually); and halonitromethanes were highest at a plant using preozonation followed by chlorine-chloramine treatment (up to 3 ppb, individually) (Richardson, 2005).

Haloacetic acids (HAAs) occur in the highest quantities after THMs and can often equal the total THM concentrations (William, *et al.,* 1997). Usually, they come from reactions between chlorine and natural organic materials (NOM), such as fulvic acid and humic acid, or some species of fatty organics (Daniel, *et al*., 2003). The formula of acetic acid is CH3COOH



DCAA

HAAs include monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid, dibromoacetic acid and bromochloroacetic acid. These are abbreviated, respectively, as MCAA, DCAA, TCAA, MBAA, DBAA & BCAA. Among specific disinfection by-products, chloroform is the predominate THM formed and dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA) occur in the highest concentrations among HAAs (William, *et al.,* 1997). The result of Nissinen *et al*., (2002) indicated that DCAA, TCAA, and chloroform were the major DBPs found in most of the DWs of Finland. Like other DBps formation of HAAs are dependent on concentration, temperature and water pH TCAA formation is maximized at a low pH but DCAA formation is essentially independent of the pH (Liang, *et al.,* 2003).

Chloramination and by products

Chloramines are generated from the reaction of chlorine with ammonia, and it appears that the length of free chlorine contact time (before ammonia addition to form chloramines) is an important factor in the formation of

iodo-acids and iodo-THMs (Plewa *et al.*, 2004). Chloramination has become a popular alternative to chlorination for plants that have difficulty meeting the regulations with chlorine. The use of chloramine as a disinfectant has increased in recent years because of limited formation of THMs; however, DBPs are emerging from the disinfection process.

The different types of chloramines are monochloramine, dichloramine, trichloramine, and organic chloramines. When chloramines are used to disinfect drinking water, monochloramine is the most common form. Dichloramine, trichloramine, and organic chloraminesare produced when treating drinking water but at much lower levels than monochloramine. Trichloramines are typically associated with disinfected water used in swimming pools.

Iodoacetic acid, one of five iodo-acids identified for the first time in chloraminated drinking water (Plewa *et al.*, 2004). Richardson (2005) put the structure of in Figure 2.

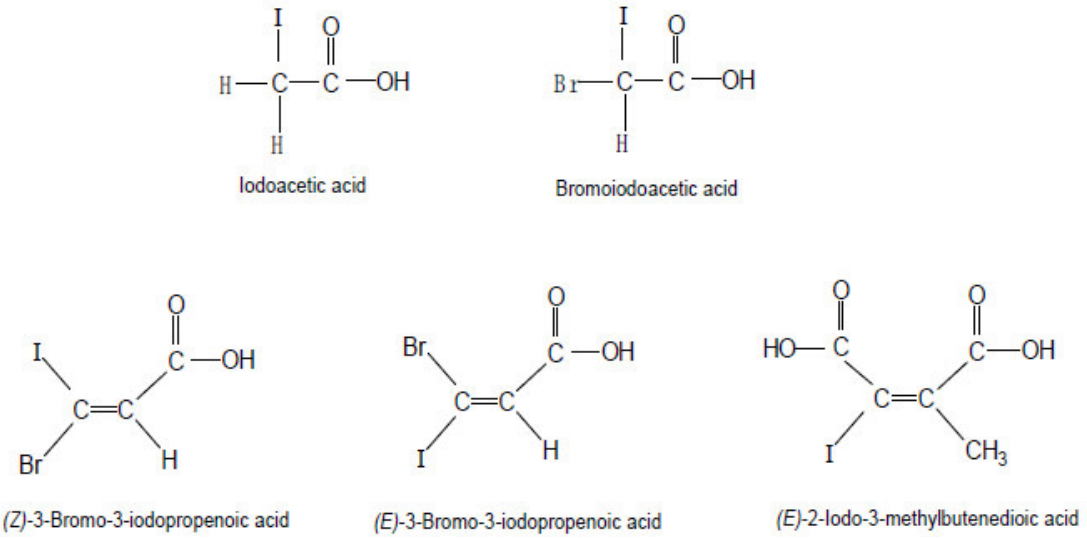


Fig. 2: Structure of newly identified Iodo-acids: Adopted from Richardson (2005).

Several of emerging DBPs are more genotoxic (in isolated cells) than many of the DBPs currently regulated, and new occurrence data have revealed that many of these DBPs can, in some cases, be present at levels comparable to regulated DBPs (Richardson, 2005).

METHODS

Search strategy and inclusion criteria

Literature was searched in different electronic data bases, such as, Pubmed, Google scholar, Cochrane library, EMBASE, HINARI and hand search conducted in English language regardless of publication date. The key words of the first step were "effect of water disinfection and disinfection byproducts". A total of eight four articles that provided information about the effect of disinfection byproduct on community, animals generally living things were reviewed. A list was produced showing name (s), part (s) and references for each.

EFFECTS OF DISINFECTION BY PRODUCTS ON HEALTH

Providing microbial safe drinking water is an important public health issue, and the use of chemical disinfection in the 20th century is rightly regarded as a major public health triumph in that regard. However, chemical disinfection has also produced an unintended health hazard the potential for cancer and other reproductive/developmental effects that may be linked to chemical disinfection by-products (DBPs) produced during disinfection (Richardson, 2005). There is substantive toxicological evidence that by-products that are produced in the disinfection of drinking water have the potential for inducing adverse health effects (Bull, 1999) (Appendix 1). Although more than 500 DBPs were identified, only a small number have been addressed either in quantitative occurrence or health effects studies (Richardson, 2005). Different mixtures of by-product may exist in different locations depending on the various factors, making it more difficult to assess any health effects of DBPs.

Earlier researches emphasized the entrance of DBPs through ingestion of the water however, new human exposure research is revealing that ingestion is not the only important route of exposure--inhalation from showering and dermal absorption (from bathing and other activities) can provide equivalent exposures or increased exposures to certain DBPs (Richardson, 2005). Among the different exposure routes (10-min shower, 10-min bath, ingesting 1 L of water), the 10- min shower produced the highest levels of THMs in the blood (from inhalation), with ingestion yielding only a slight increase in blood levels. DBP research has entered an

entirely new phase. Cancer is still important, but it is now not the only health endpoint detected in epidemiologic studies. Also, new DBPs besides the traditional regulated THMs (and HAAs) are beginning to be addressed in quantitative occurrence studies and toxicity/epidemiologic studies/risk assessments (Richardson, 2005).

Effect on experimental animals

Although chlorination of drinking water as a means of disinfection has often been considered one of the most effective public health measures instituted, it produces hundreds of disinfection by-products (DBPs), many of which are toxic and carcinogenic in experimental animals (Komulainen, 1997). The study conducted by Mcdorman *et al.,* (2003) on experimental rat suggested that DBPs can influence the development of preneoplastic lesions in the colon (ACFincidence) and enhance transitional epithelial cell proliferation in the urinary bladder of rats. The halogenated furanone MX appeared to be the predominant chemical that induced the development of urinary bladder epithelial hyperplasia and cell proliferation, and had the greatest effect on aberrant crypt foci ACF incidence in the large intestine of rat.

They hetrogenated Male and female Long-Evans rats for a germline insertion mutation in the *Tsc2* tumor suppressor gene (Eker rats) and treated with low or high doses of potassium bromate (KBrO3), 3-chloro-4- (dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX), chloroform, and bromodichloromethane (BDCM) alone or in a mixture. Similar study was carried out by Smith *et al* (1986) conducted a research on 24 experimental rats and the study was performed in two phases. In the prenatal phase, groups of 24 pregnant rats received either a blank control, un chlorinated humic rich water, or chlorinated humic rich water from day 1 of gestation until birth. The concentration of humic material was 0.8 g/L, and the pH was about 3.5. In the second phase of the study, the dams continued to drink humic rich material after parturition, and their pups received the same substances by oral intubation at a dose of 0.01 mL/g body weight from

Postpartum day 6 to day 21. Thereafter, the pups drank humic-rich waters until sacrifice at day 41. For the sec-one phase, the humic materials were prepared at 1.0g/L and neutral pH. Neither the prenatal nor the combined pre and postnatal exposures resulted in statistically significant Changes in any of the parameters measured, namely, pup number and weight. However, beginning at weaning, postnatal growth retardation was seen in chlorinated humics. Smith *et al.* (1986**)** also studied on THMs specially the toxicity of chloroform on reproduction and at the highest doses, which produced adverse clinical effects in the females, both oral and inhalation studies showed some evidence of embryotoxic or fetotoxic effects, taking the form of reduced fetal size and weight, and retarded skeletal ossification.

Disubstituted haloacid byproducts of drinking water disinfection such as dibromoacetic acid and dichloroacetic acid have been shown to perturb spermatogenesis and fertility in adult male rats (Klinefelter, *et al.,* 2002). In addition, they observed an increased incidence of delayed spermiation in the testes of males exposed to 72 mg/kg BCA for fourteen days. In the definitive study, exposures ranged from 8 (The lowest the dose for the definitive study) to 72 mg/kg, the fertility of cauda epididymal sperm was evaluated by *in utero* insemination, and the two-dimensional profile of cauda sperm membrane proteins was evaluated quantitatively. The morphology of both caput and cauda epididymal sperm was altered by 72 mg/kg BCA. The fertility of cauda epididymal sperm, the percentages of progressively motile sperm and progressive tracks, and two sperm membrane proteins (SP22 and SP9) were decreased significantly by each bromochloroacetic acid (BCA) exposure. The study done by George et al, (2000) on one month Fischer 344 rats (1g/L DCA, BCA or DBA were provided up to 5 weeks) in order to determine if a carcinogenic dose of DCA and relative concentration of BCA and DBA alter the intestinal microbial populations and their metabolism, with emphasize on the enzymes often involved in the bioactivation of procarcinogenes and promutagens and their result revealed that all three of the haloacetic acids significantly depressed body weight by 3 of treatments. However by week 5, only DBA treated animals remained affected. Small intestine weights were significantly affected. In addition, rats treated with DCA for 5 weeks, significant reduction were seen in the non-lactose fermenting entrobacteria and entrococci populations of the small intestine, accompanied by a significance increase in the total anaerobic count in the large intestine and they observed no alteration of the microflora in BCA treated rats. Regarding enzymatic alteration, they observed significant reduction of cecal β-glucoronidase (GLR) at weeks 1 and 3 by BCA and DBA treatment whereas; β-galactosidase (GAL) activity was significantly depressed at week 1 and 3 by all the three haloactic acids. Cecal azoreductase (AR), nitroreductase (NR) and dechlorinase (DC) were also depressed by the disinfection by-products. They explain their reasons as haloacetic acids may induce or repress mucosal enzymes; haloacetic acids may alter the activities in specific populations without changing the actual number of microorganisms to through enzyme repression or induction.

Carcinogenic activities of disinfection by products were also studied by different authors on experimental animals and got evidenced result. Tao *et al.*, (2005) evaluated chloroform, BDCM, DCA, TCA, and DBA for their ability to induce hypomethylation of DNA and of the c-mycprotooncogene in male mouse and rat kidneys as well as the ability of methionine to prevent the hypomethylation in mouse kidney. Their result revealed that Chloroform, BDCM, DBA, DCA, and TCA decreased the methylation of DNA and/or the c-myc

gene in mouse and/or rat kidney which indicates the epigenetic activity of disinfection by-products on kidney. DCA (3.20 g/l) and TCA (4.00 g/l), but not chloroform (1.00 g/l) significantly reduced renal DNA methylation. DCA and TCA caused 40 and 65% reduction of DNA methylation respectively in male rats. However, neither DCA or TCA nor chloroform significantly altered renal DNA methylation in female mouse kidneys. Neurotoxicity impacts of Dibromoacetic acid (DBA at 0, 0.2, 0.6, and 1.5 g/l) was studied by (Moser*, et al,* 2004). They observed the neurobehavioral alterations with DBA were of mild to moderate severity. Furthermore, grip strength was decreased approximately 25–35% throughout the study. In addition, DBA produced neural degeneration, as well as neuronal vacuolization. They observed no brain lesions or gliosis. Moreover, they observed intracellular vacuoles in the spinal cord section from mid to high concentration animals. They suggested that a component of the overall nerve fiber degeneration associated with DBA treatment.

The study conducted on impact of MX on rats showed as it is carcinogenic. High dose 70.0µg/mL of MX in the drinking water showed, increased adenomas of the adrenal glands in both sexes, increased alveolar and bronchiolar adenomas of the lungs and Langer hans' cell adenomas of the pancreas in males and increased lymphomas, leukemias, and adenocarcinomas and fibroadenomas of the mammary glands in females. They noted that even lowest 5.9 µg/mL 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) dose was carcinogenic (Komulainen, 1997).

The study conducted by Nartsocky, *et al.* (2012) provided no evidence of an effect on pregnancy maintenance on rats. The absence of an effect in their study may have been due to the different mode of administration (drinking water vs. gavage) or the much lower doses administered. In contrast, although Chlorine/Concentration did not affect pregnancy maintenance in timed pregnant (F344) rats, it did result in an increased litter incidence of eye malformations (anophthalmia, microphthalmia) compared to historical controls in this strain.

Reproductive and developmental effects

In recent years by-products have been scrutinized as a potential reproductive and developmental hazard (Chad, *et al*., 2005). Exposure to chlorinated water containing natural organic matter may result in complex mixtures with many potential causes of adverse reproductive effects (Jakkola, *et al*., 2001). Reproductive health outcomes should be easier to study from an exposure point of view, because of the shorter relevant exposure period (Nieuwenhuijsen, 2005). Birth weight, prematurity, spontaneous abortion, congenital anomalies somatic parameters at birth, neonatal jaundice and stillbirth, ventricular septal defects, cleft palate, and anencephalus have been related with DBPs. Overall there appears to be some evidence for a relationship between chlorination by-products, as measured by THMs, and small for gestational age (SGA)/intrauterine growth retardation (IUGR) and preterm delivery, Sperm quality (Kanithiz, *et al.,* 1996; Reif, *et al*., 1996; Wright et al 2004; King, *et al.,* 2005, Chad *et al*, 2005; Lewis *et al*., 2006; Savtiz, *et al*., 2006; Luben, *et al*., 2007; Hoffman, *et al.,* 2008; Chisholm *et al.,* 2008; Hwang *et al*., 2008; Rghi, *et al*., 2012.). Moreover, Rghi, *et al*., (2012) observed the most frequent anomalies were major cardiac defects, followed by chromosomal anomalies, and urinary tract defects. However, they have A little evidence of association With THMs. They investigated statistically significant increased risks, mainly for urinary tract defects, cleft palate, spina bifida and abdominal wall defects were observed in mothers exposed during pregnancy to high levels of chlorite or chlorate.

The result of Savtiz, *et al.,* (2006) revealed that women who consumed five or more glasses of cold tap water per day containing 75 µg/liter of THM4 were at increased risk of pregnancy loss (odds ratio ¼ 1.8, 95 percent confidence interval: 1.1, 3.0). Women who consumed five or more glasses per day of cold tap water containing at least 18µ g/liter of one of the THM species, bromodichloromethane, showed a more pronounced increased risk (odds ratio ¼ 3.0, 95 percent confidence interval: 1.4, 6.6).

Infants are considered at high risk to the effects of drinking water disinfected with chlorine dioxide (Kanithiz, *et al.,* 1996) because they have shortage of antioxidants (Corri *et al.*, 1982). The defense and/or adaptative processes against oxidant stress are deteriorated in women who have been drinking water treated with chlorine dioxide over a longer period of time and therefore the effects on the fetus during pregnancy are more relevant (Kanithiz, *et al.,* 1996).

Consumption of drinking water treated with chlorine dioxide may be associated with adverse effects on the hemopoietic system and also with embryotoxicity (alterations of fetal development and neonatal growth). Hoffman *et al*, (2008) supported that high levels of total trihalomethane exposure during pregnancy may actually be related to decreased risk of preterm birth and associated with delayed birth through the term period of gestation (37–40 weeks). This result is in line with the result of (Wright*, et al* 2004). They observed an association between elevated trihalomethanes with increases in gestational duration and a reduced risk of preterm delivery. They found evidence of an exposure response effect of trihalomethanes on risk of small for gestational age (SGA), with odds ratios (ORs) ranging from 1.09 to 1.23 for bromodichloromethane exposures > 5 µg/L. In addition, They observed reduction in mean birth weight for individual THMs, MX, and mutagenic activity Compared with TTHM levels < 50th percentile (≤ 33 µg/L), exposures in the 50th–90th percentiles (> 33

to 74 µg/L) and those > 90th percentile (> 74 µg/L) were associated with 12-g (95% CI, –16 to –7) and 18-g (95% CI, –26 to –10) reductions in birth weight, respectively. Similar associations were observed for chloroform (> 20 µg/L), whereas smaller effects were observed for BDCM (> 5 µg/L). Lewis *et al* (2006) also reported the effects of trimester specific and pregnancy average exposures to total trihalomethane in drinking water on term low birth weight in all singleton births. A high average total trihalomethane exposure (≥70 µg/liter) during the second trimester increased the risk of term low birth weight (odds ratio ¼ 1.50, 95% confidence interval (CI): 1.07, 2.10). Moreover they found evidence for a second-trimester and whole-pregnancy exposure to disinfection by-products and effect on fetal growth that may differ by race/ethnicity.

King *et al*., (2005) examined the relation of HAA exposure after controlling for THM exposure. In the analysis of exposure to each HAA by-product without adjustment for THMs, a relative risk greater than 2 was observed for intermediate exposure categories for total HAA and DCAA measures. However, after adjustment for total THM exposure none of the HAA measures examined was associated with stillbirth risk.

Chisholm *et al.,* (2008) reported that Women living in high TTHM areas at the time of birth of their child showed an increased risk of any Birth defect (adjusted OR = 1.22; 95% CI, 1.01–1.48) compared with women living in low TTHM areas. For individual BDs, they identified a significantly elevated OR for any cardiovascular Birth defect (adjusted OR = 1.62; 95% CI, 1.04–2.51) for women living in high TTHM areas compared with women living in low TTHM areas. Women living in high TTHM areas in Perth at the time of birth of their baby have a 22% greater risk of having a baby with any BD. More specifically, classification in the high-exposure group is associated with an increased risk of 62% for having a baby with a cardiovascular defect. Their study showed no significance result for nervous system defect (Table 1).

Table 1: ORs (95% CIs) for the association between TTHM exposures and any BD or individual BD, 2000–2004 inclusive (after Chisholm *et al.,* 2008)

Birth outcome[a]	Case number[b]	Adjusted OR (95% CI)[c]
Any BD		
Low	134	1.00
Medium	235	0.98 (0.75–1.28)
High	728	1.22 (1.01–1.48)*
Cardiovascular (BPA 74500–74799)		
Low	24	1.00
Medium	55	1.00 (0.55–1.81)
High	181	1.62 (1.04–2.51)*
Musculoskeletal (BPA 75400–75699)		
Low	29	1.00
Medium	53	1.05 (0.60–1.83)
High	200	1.48 (0.99–1.21)
Gastrointestinal (BPA 74900–75199)		
Low	11	1.00
Medium	24	1.27 (0.55–2.96)
High	66	1.20 (0.63–2.30)
Urogenital (BPA 75200–75399)		
Low	40	1.00
Medium	76	1.09 (0.68–1.77)
High	38	1.08 (0.41–2.85)
Respiratory system (BPA 74800–74899)		
Low	2	1.00
Medium	3	1.06 (0.13–8.87)
High	12	0.88 (0.18–4.18)
Integument congenital anomalies (BPA 75700–75799)		
Low	13	1.00
Medium	15	0.91 (0.36–2.33)
High	8	0.95 (0.49–1.83)

[a]Low, < 60 µg/L; medium, > 60 to < 130 µg/L; high, ≥ 130 µg/L. [b]Total births for each exposure area: low, 2,944; medium, 4,748; high, 13,178. [c]Adjusted for maternal age and socioeconomic status.
*$p < 0.05$.

The recent study and the first by its type Prelabor rupture of membranes (PROM) were studied by Joyce, *et al* (2008). The study was carried out in order to assess the relative effects of environmental agents, specifically drinking water disinfection by-products, on term PROM. The result of the study revealed that increasing exposure to nitrate in drinking water is significantly associated with an increased risk of PROM. However, they

observed no association between trihalomethanes and risk of PROM. However other studies did not support the association between chlorination and health outcomes. For instance Jakkola, *et al*. (2001) on their study found no association between foetal growth and exposure to chlorinated surface water containing natural organic matter during pregnancy. They observed that risk of low birth weight was related to neither the high chlorination nor high color alone and found no increase in the risk of preterm delivery related to exposure to chlorinated high color tap water.

Chad *et al*. (2005) in their study on effect of trihalometane and haloacetic acid on risk of fetal growth, also were not able to demonstrate any consistent, statistically significant effect on intrauterine growth retardation (IUGR) did not associate with any of the CDBPs, nor did they find any indication of a dose response relation. They did find some potential for a slightly elevated risk of IUGR during the second and third trimesters. Specifically, there was a statistically significant elevated risk of IUGR for those exposed to higher levels of HAA5 in the third trimester and a non-significant elevated risk for those exposed to higher levels of TTHM during the same period. Moreover Analysis of HAA5 constituents demonstrated a statistically significant elevated risk with exposure to bromoacetic acid in the second trimester and a non-significant elevated risk with exposure to chloroacetic acid during the same period. In addition Exposure to higher levels of dichloroacetic acid and trichloroacetic acid in the third trimester also showed a non-significant elevated risk of IUGR. Inconsistency was exhibited in their result and this is may be due to an actual lack of an effect of CDBPs on IUGR, a problem of exposure misclassification in their study population, or a lack of power in their study sample. It is hypothesized that insult prior to the third trimester may hamper fetal growth during this important time by interfering with cellular division (which predominately occurs prior to the third trimester) (Prada, *et al*, 1998). It is also reported that decreased in sperm quality do not associated with DBPs Except for total organic halide (TOX) (Luben, *et al*., 2007).

Carcinogenicity

Since the discovery of the first DBPs, a number of epidemiologic studies have evaluated the cancer risk associated with this exposure. Various studies reported the relation between cancer and drinking water which is disinfected by disinfectants. Some epidemiological studies have shown an association between long-term exposure to chlorination by-products and increased risk of cancer which is supported by experimental evidence of carcinogenicity for some of these chemicals (Richardson, *et al.,* 2000). The drinking water disinfection by-products are non genotoxic carcinogens with apparently differing potencies in the kidney (Tao, *et al*., 2005). Carcinogens are generally considered to increase the risk of cancer by two different mechanisms: genotoxic and epigenetic mechanisms. DNA methylation is a fundamental epigenetic process that not only modulates gene transcription, but is also a key to histone acetylation and chromosomal stability (Tao, *et al*., 2005). More studies have considered bladder cancer than any other cancer and bladder is one of the cancer sites associated with chlorinated water intake.

Cristina *et al*., (2007) found an increased risk of bladder cancer associated with estimates of DBP exposure from ingestion of drinking water, dermal absorption, and inhalation while showering, bathing, and swimming in pools. A doubling of the risk for bladder cancer was associated with exposure to DBP levels of about 50 mic.g/liter, commonly found in industrialized societies. Risks tended to be higher for exposure through showering, bathing, and swimming in pools compared with drinking of water. The pool analysis result of Cristina *et al*., (2004) revealed that duration of exposure to chlorinated surface water was associated with an increase in bladder cancer risk among men whereas among women, no association was observed (Table 2).

Table 2: Pooled analysis of bladder cancer and THM after (Cristina, *et al*.2004)

THM exposure level (mg)	Male ORs (95%CI)	Female ORs (95%CI)
0–15	1.00	1.00
>15–50	1.22 (1.01–1.48)	0.92 (0.65–1.32)
>50–400	1.28 (1.08–1.51)	0.94 (0.70–1.27)
>400–1000	1.31 (1.09–1.58)	1.02 (0.74–1.41)
>1000	1.50 (1.22–1.85)	0.92 (0.65–1.30)

OR (95%CI) = odds ratio (95% confidence interval).

Khalid *et al*. (2005) found that chronic myelocytic leukemia had positive associations with nearly all of the studied chlorination disinfection by-product variables. Duration of exposure seems to be an important component of chronic myelocytic leukemia risk. Moreover they concluded that the risk of adult leukemia varies

according to exposure to different types of chlorination disinfection by-products. Total trihalomethanes and bromodichloromethane may be particularly important in the etiology of chronic myelocytic leukemia.

Howe ever, there is little evidence for an association between exposure to DBPs and other cancers such as liver, kidney, brain, lung and breast cancer, lymphomas, cancer of the pancreas, but the number of studies is small (IPCS, 2000; Minh *et al*., 2008).

Allergic and Respiratory effect

In recent years, several epidemiological studies have suggested that attending chlorinated swimming pools during childhood is a risk factor for developing asthma and other allergic diseases. For instance Voisin *et al.* (2010) in Belgium examined a total of 430 children (47% female; mean age 5.7 yrs) in 30 kindergartens and reported that attendance at indoor or outdoor chlorinated pools ever before the age of 2 yrs was associated with an increased risk of bronchiolitis. Moreover they reported as infant swimmers who developed bronchiolitis also showed higher risks of asthma and respiratory allergies later in childhood. Swimming pool attendance during infancy is associated with a higher risk of bronchiolitis, with ensuing increased risks of asthma and allergic sensitisation. The result of Bernard *et al*. (2007) is in line with the above result which shows that the infant swimming practice is associated with lung epithelium alterations that seem to predispose children to the development of asthma and recurrent bronchitis later in childhood. The underlying hypothesis is that exposure to disinfectants and disinfection by-products in the swimming pool (probably trichloramine, a strong irritant may cause a detrimental effect in the airways of children with a consequent increased risk of developing asthma (Bernand, *et al*., 2007). The result of Ribera *et al*. (2009) and (2011) deviated from the above result as swimming did not increase the risk of asthma, atopy, or any respiratory and allergic symptom in British and Spain children. However attendance at both indoor and outdoor swimming pools was associated with an increased prevalence of eczema in children of Spain. There are several possible explanations for real different effects among areas. First, different patterns of swimming pool attendance in children resulting in different cumulative exposures. Second, there may be differences in the level of trichloramine or other irritants in the swimming pools. Third, uncontrolled confounding variables (e.g., physical activity) may be different. Finally, there may be differences in the presence and extent of reverse causation (i.e., children with asthma attending or avoid swimming pools (Ribera, *et al*., 2011).

Genotoxicity and Mutagencity

Kogevans *et al.* (2010) in their study on Genotoxic Effects in Swimmers Exposed to Disinfection Byproducts in Indoor Swimming Pools, observed that a small but statistically significant decrease in the average amount of DNA damage in blood lymphocytes after swimming relative to before swimming (Table 3). They also observed increment of urine mutagencity after swimming in association with the concentration of exhaled $CHBr_3$

Table 3: Change in mean values of biomarkers before and after swimming, peripheral blood lymphocytes (PBL) and urine After (Kogevinas *et al.*, 2010)

	No. of subjects		Mean value ± SD		
Biomarker[a]	Before	After	Before	After	*p*-value[b]
MN-PBL	49	49	3.4 ± 2.4	4.0 ± 2.8	0.235
OTM-Comet-PBL	49	49	1.5 ± 0.7	1.3 ± 0.6	0.008
MN-urothelial cells	33	33	9.0 ± 9.3	10.3 ± 7.4	0.350
Urine-mutagenicity	43	43	0.6 ± 2.3	1.2 ± 2.2	0.257

[a]MN-PBL: Micronucleated cells per 1000 binucleated cells; OTM-Comet-PBL: Olive tail moment per 100 cells; MN-urothelial cells: micronucleated cells per 2000 cells; Urinary mutagenicity: Rev/ml-eq.

[b]Paired t-test.

CONCLUSION

Various studies were conducted on the impact of DBPs on human health. Especially impacts on reproductive,

cancer and respiratory and allergy were studied. Studies conducted on cancer showed that there is no much evidence or consistency among them. However, positive associations were found between DBPs and bladder cancer. There was little support on pancreatic cancer. Regarding reproduction, the result is mixed mean that some get positive association and others reported that there is negative association between DBPs and reproduction. Mixed results were reported about the impact of DBPs on respiratory and allergy. Studies from Belgium got that higher exposure to DBPs result in increment risk of bronchiolitis, asthma and lung epithelium alteration. Other studies conducted elsewhere such as Spain reported that there is no association between swimming in chlorinated water and respiratory defect and allergy even they reported as swimming is recommended for asthma. Assessment on exposure, biasness and sample size may be the cause for inconsistency of the findings. In addition to this much of the studies only focus on THMs and HAA therefore; researchers should focus on emerging DBPs. In order to analyze the impact thoroughly moreover this inconsistency may arise due to DBPs type and level of carcinogens.

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