ESTIMATION OF TOTAL CARCINOGENIC RISK DUE TO MULTIPATHWAY EXPOSURE TO TRIHALOMETHANES IN İZMİR DRINKING WATER

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This thesis is for my father İbrahim Ülkü ERGİ, I hope he is watching me and proud of me.

ABSTRACT

ESTIMATION OF TOTAL CARCINOGENIC RISK DUE TO MULTIPATHWAY EXPOSURE TO TRIHALOMETHANES IN İZMİR DRINKING WATER

The goal of this study was to investigate the cumulative and total carcinogenic risk levels of trihalomethanes (THMs) in İzmir drinking water by considering multi exposure routes and pathways. Drinking water THM concentrations measured and questionnaire data collected by Kavcar (Assessment of Exposure and Risk Associated with Trihalomethanes and Other Volatile Organic Compounds in Drinking Water, MSc Thesis, İYTE, 2005) were used for the exposure – risk assessment. Ingestion of drinking water, inhalation and dermal absorption during showering, bathing, hand washing, and dish washing were the considered exposure pathways.

THM concentrations in air were estimated by using chemical specific transfer efficiencies. Chemical specific skin permeability coefficients and body surface areas were used . The contributions of exposure routes to the total risk, in the order of low to high, were dermal absorption, ingestion, and inhalation.

Cumulative and total cancer risks were estimated using two different methods: commonly employed simple addition method and recently proposed Cumulative Relative Potency Factors (CRPF) approach. The total carcinogenic risks estimated by the both methods were acceptable ($<1\times10^{-6}$) in the minimum and lower bound exposure scenarios, generally acceptable (1×10^{-6} - 1×10^{-4}) in the central tendency exposure scenario, and not acceptable ($>1\times10^{-4}$) in the upper bound and maximum exposure scenarios while simple addition produced an order magnitude higher risk levels compared to the CRPF method. The results of this study show that carcinogenic risks may be overestimated by using simple addition method. Nevertheless, risk mitigation measures are needed by the local water authorities.

ÖZET

İZMİR İÇME SUYUNDAKİ TRİHALOMETANLARA ÇOKYOLLU MARUZİYET SONUCU OLUŞAN TOPLAM KANSER RİSKİNİN BELİRLENMESİ

Bu çalışmanın amacı, çeşitli maruziyet yollarını içerecek şekilde, İzmir içme suyunda trihalometanların (THM) kümülatif ve toplam kanserojen risk seviyelerini araştırmaktır. Maruziyet ve risk değerlendirilmesinde, Kavcar (Assessment of Exposure and Risk Associated with Trihalomethanes and Other Volatile Organic Compounds in Drinking Water, MSc Thesis, İYTE, 2005) tarafından içme suyunda ölçülen THM konsantrasyonları ve anket sonuçları kullanılmıştır. Maruziyet kaynakları olarak içme suyunun tüketimi, duş, banyo, el yıkama ve bulaşık yıkama sırasında soluma ve deri ile etkileşim düşünülmüştür.

İçme suyunda bulunan THM konsantrasyonu ölçülmüş değerlerdir. Havada bulunan THM konsantrasyonu ise kimyasallara özgü transfer etki katsayıları kullanılarak hesaplanmıştır. Deri maruziyetlerinin hesaplanmasında kimyasala özgü deri geçirgenlik katsayıları ve vücut yüzey alanları kullanılmıştır. Maruziyet yollarının toplam riske katkısını düşükten yükseğe doğru dizecek olursak deri, yeme ve soluma şeklide olmaktadır.

Kümülatif ve toplam kanser riski 2 farklı metot ile hesaplanmıştır. Bunlar; genellikle uygulanan basit toplama metodu ve son zamanlarda yayınlanan Kümülatif İlgili Potansiyel Faktör (CRPF) yaklaşımıdır. Her iki yöntem ile uygulanan toplam kanser riski en düşük ve alt seviye senaryolar için kabul edilebilir ($<1\times10^{-6}$) seviyededir. Ortalama senaryosu için genel kabul edilebilir (1×10^{-6} - 1×10^{-4}) seviyededir. En yüksek ve üst seviye senaryolar için kabul edilemez ($>1\times10^{-4}$) seviyededir. Basit toplama yöntemi CRPF yönetimi ile karşılaştırıldığında daha yüksek risk seviyelerini göstermektedir. Bu çalışmanın sonucu bize basit toplama yönteminin, riskleri daha yüksek seviyelerde göstereceğini anlatmıştır. Buna rağmen, yerel otoritelerin riski azaltıcı önlenmelere ihtiyaçları vardır.

TABLE OF CONTENTS

LIST OF FIGURES

Figure **Page**

LIST OF TABLES

Figure **Page**

LIST OF ABBREVIATIONS

AT:	Averaging Time
BSA:	Body Surface Area
BW:	Body Weight
C:	Contaminant Concentration
CDI:	Chronic Daily Intake
CF:	Conversion Factor
CRPF:	Cumulative Relative Potency Factor
D:	Exposure Dose
DBP:	Disinfection by Products
ED:	Exposure Duration
EF:	Exposure Factor
F:	Frequency of Exposure
HI:	Hazard Index
HQ:	Hazard Quotient
ICED:	Index Chemical Equivalent Doses
IR:	Intake Rate
IRIS:	Integrated Risk Information System
K:	Overall Mass Transfer Coefficient
K_ps:	Permeability Coefficient
LT:	Life Time
MOA:	Mode of Action
R_T:	Total Risk
RfD:	Reference Dose
RPF:	Relative Potency Factors
SA:	Exposed Body Surface Area
SF:	Slope Factor
THM:	Trihalomethanes
TTHM:	Total Trihalomethanes
USEPA:	United States Environmental Protection Agency
VOC:	Volatile Organic Compounds
Φ:	Transfer Efficiency

CHAPTER 1

INTRODUCTION

The use of chlorine in the treatment of drinking water has virtually eliminated waterborne diseases, because chlorine can kill or inactivate most microorganisms commonly found in water. However, the use of chlorine can lead to the formation of disinfection by-products (DBP) such as THMs (Stiteler et al., 2000). Trihalomethanes (THMs) are a group of compounds which are formed in drinking-water primarily as a result of chlorination of organic matter present naturally in raw water supplies (e.g., decaying leaves and vegetation).

Volatile organic compounds such as THMs have adverse health effects. Liver and kidney damage, immune system, nervous system, reproductive system and several types of cancers may occur because of exposure to drinking water containing volatile organic compounds (VOC). Also the exposure to DBPs increases the risk of bladder, colon-rectum, leukemia, stomach and rectal cancers as well as abortion, birth weight and birth defects (Cantor 1997, Calderon 2000). Chloroform ($CHCl_3$) is the most common THM, detected in the greatest concentrations in water. The U.S. Environmental Protection Agency (USEPA) has classified chloroform as a probable human carcinogen (http://www.epa.gov/iris). High dose of chloroform is a carcinogen (Lévesque et al., 2000). However, chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration (Nazir et al., 2005). Eventually, USEPA has withdrawn ingestion carcinogenic potency factor for chloroform because its levels are generally low in drinking water (http://www.epa.gov/iris).

The trihalomethanes consists of chloroform ($CHCl_3$), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform ($CHBr_3$). It is assumed that the primary exposure route to THMs is ingestion. However, THMs are volatile organic compounds and may be transferred to air, depending on the environmental conditions, which results in inhalation and dermal exposures. Drinking water exposure to THMs may occur by four pathways:

- Ingestion of drinking-water,

- Inhalation of indoor air largely due to volatilization from drinking-water,
- Inhalation and dermal exposure during showering or bathing
- Ingestion of food, with all but food exposure arising primarily from drinking-water

Exposure assessment is a main component of the risk assessment process. Exposure to THMs depends on human activity and water use patterns and DBP concentrations in water. After exposure, pharmacokinetics and pharmacodynamics determines the dose. Pharmacokinetics incorporates information on organ volumes, organ-specific blood flows and metabolic capacity. Generally, no pharmacokinetic interactions among mixture components are assumed (Teuschler et al., 2004). Figure 1.1 shows the relations among pollutant concentrations, exposure, and dose.

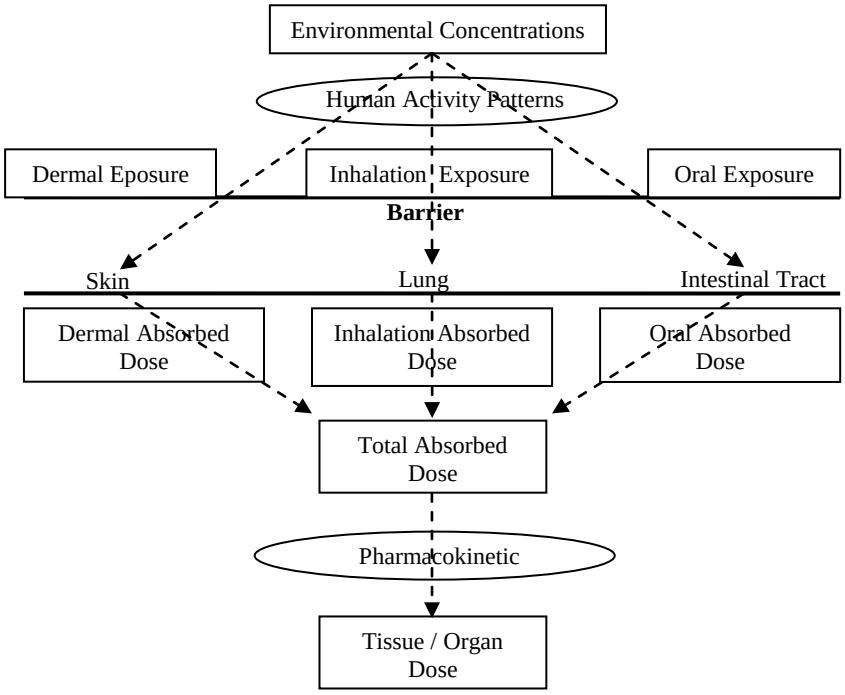

Figure 1.1. Dose Metrics for Environmental Concentrations
(Source: Teuschler et al., 2004)

Dose can be measured by four different ways. In the body, there are exchange boundaries such as skin, lung and intestinal tract. (1) Route-Specific Exposure occurs when that amount of a chemical available to pass the boundary. (2) Route-Specific Absorbed Dose is the amount of a chemical which is absorbed from a single exposure route. (3) Total Absorbed Dose is the amount of a chemical which is absorbed from all

exposure routes. For example, amount of chemical in blood. (4) Organ or Tissue Doses are the amount of a contaminant in an organ or tissue (Teuschler et al., 2004), which causes the health effect.

Risk is determined for individual chemicals. Aggregate exposure and risk assessment involve the analysis of exposure to a single chemical by multiple pathways and routes of exposure. Cumulative exposure and risk involve assessment for multiple chemicals in a mixture over one exposure route. Aggregation of cumulative exposure-risk over multiple exposure routes results in the total risk. Generally to calculate cumulative risk in a mixture, the risk of contaminants for each route is simply added together. This approach is called Simple Additive Method.

Complex mixtures such as those resulting from disinfection of drinking water supplies present a difficult problem for risk assessors because of the large number of components. The concentration of each individual component may be small enough to pose no threat, but if they act jointly in some additive or greater than additive manner, then there may be some concern for health safety (Krishnan et al., 1997). To calculate cumulative risk for a mixture, simple addition can only be applied if the mode of action, the mechanism of the health effect, is similar for individual components of the mixture. Teuschler et al. (2004) proposed a cumulative risk assessment method, the Cumulative Relative Potency Factors (CRPF) approach which combines exposure modeling and physiologically based pharmacokinetic modeling results. Carcinogenic risks of THMs for İzmir drinking water were estimated (Kavcar et al., 2006; Baytak et al., 2008) but for only ingestion route. This study aimed to estimate cumulative and total risk levels for THMs for İzmir drinking water using the approach proposed by Teuschler et al. (2004).

This thesis includes seven chapters. Chapter 1 presents a brief introductory background to the research subject. Previous relevant studies are reviewed in Chapter 2. Carcinogenic risk assessment is presented in Chapter 3. Material and methods are described in Chapter 4. In Chapter 5, the results of CRPF approach is presented. The discussion of the study is summarized in Chapter 6. Finally, the main results and the conclusions of the study are followed by in Chapter 7.

CHAPTER 2

LITERATURE REVIEW

2.1. THM Concentrations in Drinking Water

THMs in drinking water have been widely studied throughout the world. Therefore there are many studies that report THM levels in drinking water from both Turkey and other countries. Since, the focus of this study is on the risk assessment for THMs only a brief review is presented here.

2.1.1. THM Concentrations in Abroad and Turkey

Legay et al. (2011) conducted a study to investigate THM concentrations in the regions of Québec and Lévis in Canada. Measured concentration ranges were reported as 14.1-155 μg/L for chloroform; 1.21-10.8 μg/L for BDCM; 0.2-3.34 μg/L for DCBM; 0.15-0.38 μg/L for bromoform. Average Total THM (TTHM) concentrations were measured between 18.6 μg/L and 158.2 μg/L with standard deviations of 8.6 μg/L and 61.4 μg/L, for Quebec and Levis regions, respectively (Legay et al., 2011).

Lee et al. (2004) analyzed tap water samples from different locations in Hong Kong for THMs. TTHM levels measured in the study varied from 15.8 to 87.2 μg/L. Chloroform was the major THM compound measured between 5.71 and 75.1 μg/L (Lee et al., 2004).

Tokmak et al. (2004) conducted a study in Ankara, Turkey. Tap water samples were collected seasonally from 22 different districts to observe occurrence of THMs. The statistics of concentrations were not reported, the following are based on the numbers extracted from the figures in the article. The average concentration for TTHM, chloroform, BDCM, the sum of DBCM and bromoform was about 45 μg/L, 40 μg/L, 4 μg/L, 1 μg/L, respectively. The TTHM concentration of the water leaving the treatment plant was measured as 35 μg/L, while it was measured as 110 μg/L at a sampling point in Konutkent district which is one of the furthest to the plant.

Uyak (2005) reported THM concentrations in Istanbul at sampling points served by different water sources. Chloroform concentrations were between of 42 μg/L and 12 μg/L; BDCM were between 30 μg/L and 11 μg/L; DBCM were between 33 μg/L and 6.7 μg/L; and bromoform were between 11 μg/L and 1 μg/L. The average measured concentrations are presented in Table 2.3.

Two studies reported THM concentrations for İzmir drinking water. Kavcar et al. (2006) collected samples from 100 different sampling points throughout the province. Baytak et al. (2008) collected 44 samples at one point in the metropolitan area to determine seasonal variation. The mean concentrations of chloroform, BDCM, DBCM, and bromoform were 4.41, 3.73, 2.61 and 0.62 μg/L, respectively, measured by Kavcar et al. (2006) with ranges from below detection limit to 35 μg/L for chloroform, 28 μg/L for BDCM, 18 μg/L for DBCM, and 4 μg/L for bromoform. However, the average concentrations (and maximum values) were much higher due to seasonal effects 22 (98), 15(66), 10(44), 5(20) μg/L for chloroform, DBCM, BDCM, and bromoform, respectively, as reported by Baytak et al. (2008).

Table 2.1. Minimum and Maximum THM Concentrations Reported in the Literature

Literature	TTHM (μg/L)		Chloroform (μg/L)		BDCM (μg/L)		DBCM (μg/L)		Bromoform (μg/L)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Legay et al., 2011										
Québec region	18.6	158.2	14.1	155.9	1.21	9.4	0.2	3.34	0.17	0.38
Lévis region	26.3	72.9	19.7	64.2	2.65	10.8	0.24	1.65	0.15	0.33
Lee et al., 2004										
Hong Kong	15.80	87.20	5.71	75.1	5.04	17.2	0.83	5.56	0.04	0.92
Uyak, 2005										
Istanbul	33	100	12	42	11	30	6,7	33	1	11
Kavcar et al., 2006										
Izmir	-	-	$3.84x10^{-11}$	34.58	$1.58x10^{-07}$	27.45	$4.09x10^{-07}$	13.48	$2.02x10^{-04}$	4.19
Baytak et al., 2008										
Izmir	2.86	183	0,03	98.39	0.01	43.82	0.19	65.91	0.04	19.13

2.2. Human Health Risk Levels Due to THMs in Drinking Water

Legay et al. (2011) conducted a study in Canada. In the assessment of cancer risk, multi-exposure routes (ingestion, inhalation and dermal contact) were considered. Showering and bathing activities for inhalation and dermal exposure; drinking water for ingestion exposure was included. Total carcinogenic risk was estimated by simple addition of carcinogenic risks of THM species. Since there was a debate over carcinogenity of chloroform, the risks were estimated with and without chloroform.

Total carcinogenic risk was calculated by simple addition method. All total cancer risk (R_T) values were $>10^{-6}$, greater than the acceptable carcinogenic risk level, when chloroform was included in the assessment. On the other hand, carcinogenic risk assessment without chloroform resulted in 5^{th} and 50^{th} percentile values of $<5.10^{-5}$. Whereas the 95^{th} percentile value ranged between 5.10^{-5} and 10^{-4} in different zones (Legay et al., 2011).

Lee et al. (2004) estimated cancer and chronic-toxic risks due to THMs in tap water in Hong Kong. All three routes (ingestion, inhalation, and dermal) were considered. Total carcinogenic risk was calculated by simple addition method. Their results indicated that ingestion was the most important route. The average lifetime cancer risks were ranked in descending order as BDCM, chloroform, DBCM, and bromoform for ingestion route with percentage contributions of 59, 24, 17, and 0 to the total risk, respectively. In all districts studied in Hong Kong, cancer risk for bromoform was $<10^{-6}$, whereas the risk levels for the other THM species exceeded this level. The lifetime cancer risks calculated for TTHMs were in the range $4.5x10^{-5}$ - $1.15x10^{-4}$ with an average value of $7.55x10^{-5}$. Table 2.4. presents the risk values reported in the literature.

Uyak (2005) conducted a multi-route exposure–risk assessment study in Istanbul. Total risk was calculated by the simple addition method. Istanbul residents had a higher risk of cancer through ingestion route. The lifetime cancer risks through oral ingestion of chloroform, BDCM, and DBCM in tap water of all the sampled districts were higher than 10^{-6}.

Tokmak et al. (2004) estimated multi-route carcinogenic risk and calculated total risk levels by simple addition for THMs in Ankara. The average lifetime cancer risk of about 1.2×10^{-5} caused by chloroform was almost 12 times higher than the acceptable

risk level of 10^{-6}. Total carcinogenic risk values were extracted from the illustrations in the article. The average risk was approximately 1.4×10^{-5}. The highest cancer risk was due to firstly ingestion, secondly inhalation and lastly dermal route (Tokmak et al., 2004).

Table 2.2. Average Cancer Risk Reported in the Studies

Literature	TTHM		Hazard Index	
Lee et al., 2004				
	Male	Female	Male	Female
Hong Kong	$9.76x10^{-5}$	9.60×10^{-5}	3.45×10^{-1}	3.45×10^{-1}
Uyak., 2005				
Istanbul	1.13×10^{-4}	1.18×10^{-4}	1.81×10^{-1}	1.87×10^{-1}
*Kavcar et al., 2006**				
Izmir	$1,33x10^{-5}$		0,0229	

*Hazard Index and TTHM were only calculated for ingestion route.

Multi-pathway evaluations of noncarcinogenic risks for THMs were calculated by using the hazard index. Hazard index of THMs is obtained through oral route and dermal absorption (Lee et al., 2004).

Table 2.3. Average Hazard Index for THM Reported in the Studies

	Hazard Index For THMs							
Literature	Oral Route		Dermal Route for Male		Dermal Route for Female		Inhalation*	
Lee et al., 2004	Min	Max	Min	Max	Min	Max	Min	Max
Hong Kong	6.89×10^{-2}	5.19×10^{-1}	2.87×10^{-6}	1.10×10^{-5}	2.5×10^{-6}	9.6×10^{-6}	1.00×10^{-6}	1.50×10^{-5}
	Oral Route for male		Dermal Route for Male		Dermal Route for Female		Inhalation**	
Uyak., 2005	Min	Max	Min	Max	Min	Max	Min	Max
Istanbul	6.43×10^{-2}	1.85×10^{-1}	2.49×10^{-2}	7.9×10^{-2}	2.34×10^{-2}	6.75×10^{-2}	-	-

* Non-cancer risk is only carried out for chloroform compound not for THMs. Because of its property of a lower boiling point, chloroform is assumed to be the major compound
**Hazard Index was not calculated for inhalation route.

Kavcar et al. (2006) and Baytak et al. (2008) estimated the risks for only ingestion route drinking water pathway. The mean deterministic noncarcinogenic risk (hazard quotient) for chloroform, BDCM, DBCM, and bromoform was 0.0128, 0.0054, 0.0038, and 0.0009, respectively. HQ values greater than 1 indicate a potential for an adverse effect to occur or the need for further study. For İzmir drinking water, however, the calculated HQ values pointed out negligible noncarcinogenic risks. The mean deterministic carcinogenic risk was estimated for the metropolitan area as 6.74×10^{-6}, for BDCM; 6.46×10^{-6} for DBCM; and 1.46×10^{-7} for bromoform. Chloroform was not included because USEPA had withdrawn its potency factor. The carcinogenic risks were higher when seasonal variations in the THM concentrations were considered (Baytak et al., 2008). The mean carcinogenic risk values were 2.5×10^{-5}, 3.5×10^{-5}, and 6.6×10^{-6} for BDCM, DBCM, and bromoform, respectively.

CHAPTER 3

CARCINOGENIC RISK ASSESSMENT

This chapter defines different types of carcinogenic risk which are risk, aggregate risk, cumulative risk, and total risk.

Risk is defined as the risk of one component for one exposure route. Aggregate risk is defined as the total risk of one component obtained by summing risks of each exposure route. Cumulative risk is obtained when the risks of all components in a mixture for one exposure route. Total risk is obtained when the cumulative risks are summed up over all exposure routes. USEPA uses a general acceptable risk value (1.0×10^{-6}) for environmental pollutants. However, depending on the state-of-the-art with regards to sampling/analytical techniques and control technologies, higher levels can be assumed as in the case of acceptable carcinogenic risk for arsenic (1.0×10^{-4}). Recently, Legay et al. (2011) categorized total risks as no action is needed ($R_T< 10^{-6}$). General acceptable levels ($10^{-6}\leq R_T < 5.10^{-5}$), low priority ($5.10^{-5}\leq R_T < 10^{-4}$), and unacceptable, action required ($R_T \geq 10^{-4}$).

3.1. Common Approach to Cumulative Risk – Simple Addition

Risks estimated for each component of a mixture is summed up to calculate cumulative and then total risks (Legay et al., 2011; Lee et al., 2004; Tokmak et al., 2004; Uyak, 2006). The equation for total carcinogenic risk is given below (Eq. 3.1).

$$\sum\sum Rij \tag{3.1}$$

where,

R = Risk

i = Polutant

j = Route

3.2. Alternative Approach to Cumulative Risk- Cumulative Relative Potency Factors

The Cumulative Relative Potency Factors (CRPF) approach as the mixtures risk assessment method was proposed by Teuschler et al. (2007), and a case study was illustrated for THMs. CRPF approach uses two different methods to estimate cumulative risk: dose addition and response addition.

In a mixture, there are different pairs of components. If there is a common mode of action or no interactions between the components, the definition of additivity may be appropriate. Dose addition and response addition depends on the toxicity similarity of chemicals.

3.2.1. Mode of Action (MOA)

For chemical mixtures, defining the similarity of toxic action has become an important first step in the risk assessment process. Substances, that cause a common toxic effect(s) by the same, or essentially the same mechanism, have the same Mode of Action. The subclasses that have different MOA, they are assumed to cause toxicity independently of each other. Mode of action means the knowledge of molecular and cellular events leading to a toxicological outcome. A toxicological outcome is considered as damaging to the organism at any level of biological organization (i.e., molecular, cellular, tissue, etc.) (Teuschler et al., 2004).

Dose addition and response addition methods can be integrated to assess risk. To estimate the risk of each subclass, the mixture's components are categorized into subclasses of the same MOA. Therefore the risk of each subclass can be estimated based on Relative Potency Factors (RPF) approach. The subclass risks can be added to yield the total mixture risk of causing the same health outcome (Teuschler, 2007).

3.2.2. Index Chemical

The index chemical, which is a component in the mixture, must have a clearly defined and high quality dose-response relationship and data. For the effect and route of concern, that component also has the same mode of action as the other members of the

subclass. For each subclass, the strength and completeness of the components' toxicity data is to be evaluated to identify an index chemical.

3.2.3. Dose Addition

The risk from exposure to multiple chemicals acting via a common MOA may be assessed using the summed doses of the individual chemicals scaled for relative potency. The dose addition is recommended for the components in a mixture that show similar toxicity (Choudhury et al., 1999).

3.2.4. Response Addition

The risk from multiple chemicals acting via independent MOA may be assessed by summing the probabilistic risks of response from exposure to the individual chemicals. The response addition is recommended for the components chemicals in a mixture that show dissimilar toxicity. To apply the dose addition or response addition method, lower exposure levels and no interaction information should be available (Choudhury et al., 1999).

3.2.5. ICED (Index Chemical Equivalent Doses)

ICED combines dose addition and response addition into one method. The Cumulative Relative Potency Factors (CRPF) approach use chemical mixture which has common mode of action subclasses. That means toxicological outcome is the same. For each subclass, an index chemical is selected. In our study there is one subclass that is THMs. First of all, the highest quality mode of action data is selected. Dichlorobromomethane (BDCM) is selected as index chemical as suggested by Teuschler (2004). Index Chemical Equivalent Dose (ICED) is calculated by using a Relative Potency Factor (RPF). Component ICED is the ICED for an individual chemical in a subclass. Subclass ICED is calculated by summing their component ICEDs (Figure 3.1).

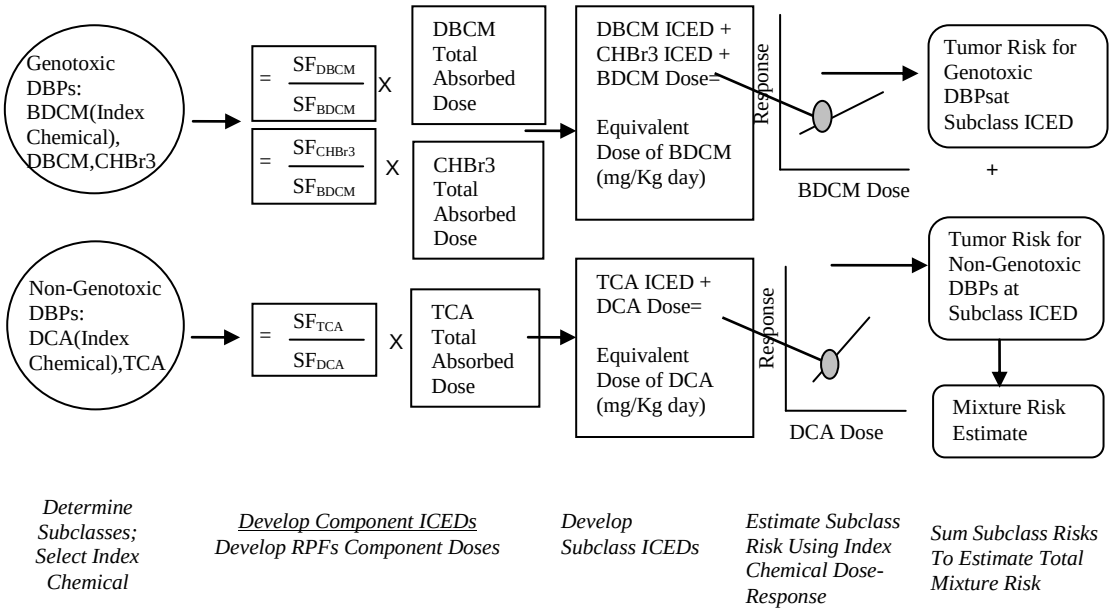

Figure 3.1. Illustration of CRPF Approach for Illustration of DBP Mixture Cancer Risk (Source: Teuschler et al., 2004)

RPF(s) are calculated by the ratio of slope factors. Slope factor of a chemical is divided to slope factor of the index chemical.

$$RPF = SF_{component} / SF_{index\ chemical} \quad (3.4)$$

The absorbed dose for each DBP is multiplied by its RPF. Therefore a component ICED for each member of the subclass is calculated.

$$\text{Component ICED} = RPF \times \text{Total Absorbed Dose of Component} \quad (3.5)$$

Sum of component ICEDs is used for obtain subclass ICED.

$$\text{Subclass ICED} = \text{Component}_1 \text{ ICED} + \text{Component}_2 \text{ ICED} + \ldots + \text{Component}_n \text{ ICED} \quad (3.6)$$

$$\text{Subclass Risk} = \text{MLE Slope Factor} \times \text{Subclass ICED} \quad (3.7)$$

$$\text{Total Mixture Risk} = \text{Subclass Risk}_1 + \text{Subclass Risk}_2 + \ldots + \text{Subclass Risk}_n \quad (3.8)$$

The approach for calculating subclass ICED is the dose addition, since the mode of action of each component is the same in the subclass. On the other hand, to calculate the total mixture risk, the approach is the response addition, because the subclasses risks, which have different mode of action, are summed together.

CRPF approach is also implemented to multiple exposure routes. CRPF analysis is conducted to separate exposures for each route. Ingestion, inhalation and dermal exposures are considered in the calculation.

CRPF approach is suitable for components which has cancer end point. Carcinogens are divided into two classes that are genotoxic and non-genotoxic. Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration. USEPA has withdrawn the cancer potency factor for chloroform because its levels are generally low in drinking water. Bromodichloromethane and bromoform are probable human carcinogens; dibromochloromethane is a possible human carcinogen (http://www.epa.gov/iris). Choloroform is non-genotoxic; while BDCM, DBCM, and bromoform are genotoxic (see Table 3.1).

Table 3.1. Carcinogenty Class of DBP
(Source: IRIS, 2005)

DBP	**Toxicity**	**Carcinogenity**
Bromodichloromethane (BDCM)	Genotoxic	Probable human carcinogen
Dibromochloromethane (DBCM)	Genotoxic	Possible human carcinogen
Bromoform ($CHBr_3$)	Genotoxic	Probable human carcinogen
Chloroform ($CHCl_3$)	Non-Genotoxic	Probable human carcinogen

CHAPTER 4

MATERIAL AND METHOD

4.1. Characteristics of Studied Participants

In this study, THM concentrations (measured in tap water samples collected from homes in metropolitan area of İzmir) and time-activity data (collected by administering questionnaires to a participant from each sampled home) collected by Kavcar (Assessment of Exposure and Risk Associated with Trihalomethanes and Other Volatile Organic Compounds in Drinking Water, MSc Thesis, İYTE, 2005) were used for cumulative risk assessment of THMs in drinking water. Participants were from the district of Güzelbahçe (1%), Balçova (3%), Gaziemir (3%), Narlıdere (3%), Çiğli (4%), Buca (13%), Bornova (18%), Karşıyaka (19%) and Konak (34%). Drinking water samples were analyzed for VOCs using an automated headspace sampler followed by a gas chromatograph (GC). The GC was equipped with a mass spectrometry (MS) detector to identify and quantify VOCs.

For each sampling unit, one person was asked to be the primary participant and administer the questionnaires. The first questionnaire, which inquired about demographics of occupants, was administered by the investigators during the visit. The second questionnaire was self-administered by the primary participant. Data collected from questionnaires such as body weight and daily intake rate, the two most important parameters to be used in estimating chronic daily exposure, were helpful in predicting more accurate risk levels compared to making assumptions, as usually practiced in risk assessment studies. Other key data included gender, age, education and income level, and homeland which made comparison of exposure and risk for different subgroups possible. The participants were also asked to provide information regarding activities that determine inhalation and dermal exposure to THMs, such as showering/bathing, dish washing, hand washing, etc. Details regarding materials and methods can be found elsewhere (Kavcar et al., 2006). Only a small portion of the participants (32) provided extended questionnaires, therefore this study was based on the data obtained for/from these participants. Information regarding participant characteristics are presented in

Table 4.1 and 4.2. Descriptive statistics for the measured concentrations (Table 4.3) and concentration frequency histograms (Figures 4.1 – 4.4) are also presented.

Table 4.1. Descriptive Statistics for Participant Characteristics – Gender

Gender	**Number**	**Percentage**
Female	21	%66
Male	11	%34

Table 4.2. Descriptive Statistics for Participant Characteristics - Age and Weight

	Median	Mean	SD	Min	Max	95th percentile
Age	28	33	12,6	16	67	52.2
Weight (kg)	67	66	14,4	47	96	87

Table 4.3. Descriptive Statistics for Measured THM Concentrations (μg/L)*

	Median	Mean	SD	Min	Max	95th percentile
Chloroform	0.10	7.65	12.1	3.84×10^{-11}	34.6	29.9
BDCM	0.13	6.29	9.82	4.76×10^{-6}	27.5	24.6
DBCM	0.42	4.31	6.32	3.24×10^{-4}	17.2	15.3
Bromoform	0.45	0.98	0.10	3.97×10^{-3}	3.22	2.5

*Censored concentrations, see Kavcar et al. (2006) for the censoring method

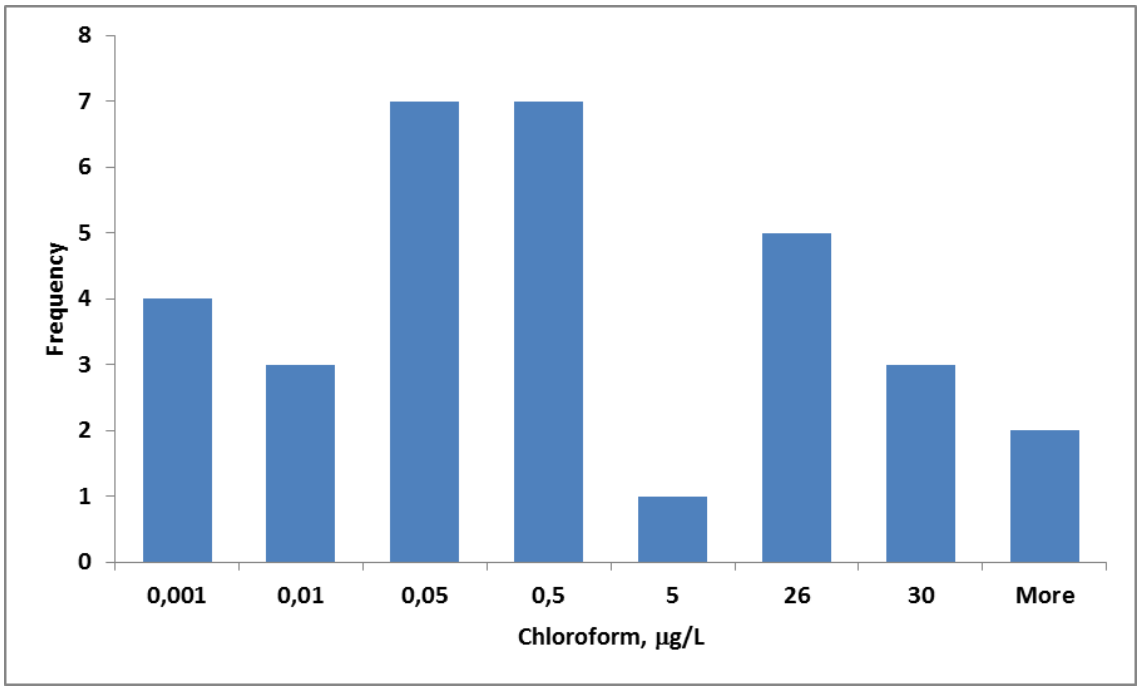

Figure 4.1. Distrubution of Chloroform Concentrations

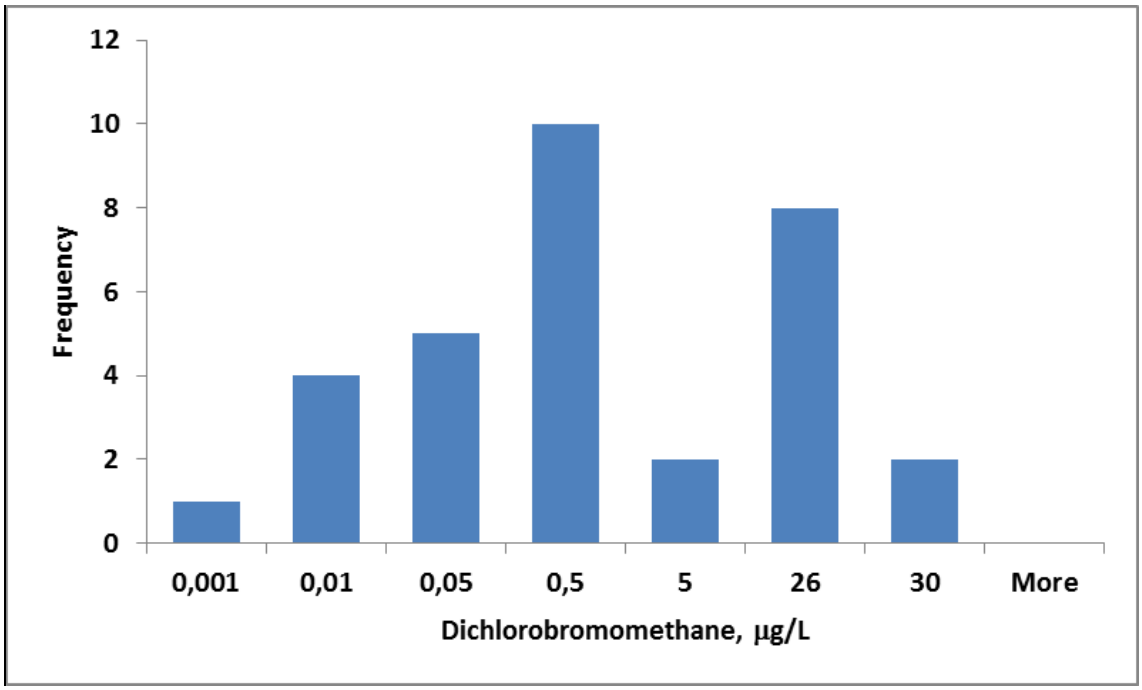

Figure 4.2. Distrubution of Dichlorobromomethane Concentrations

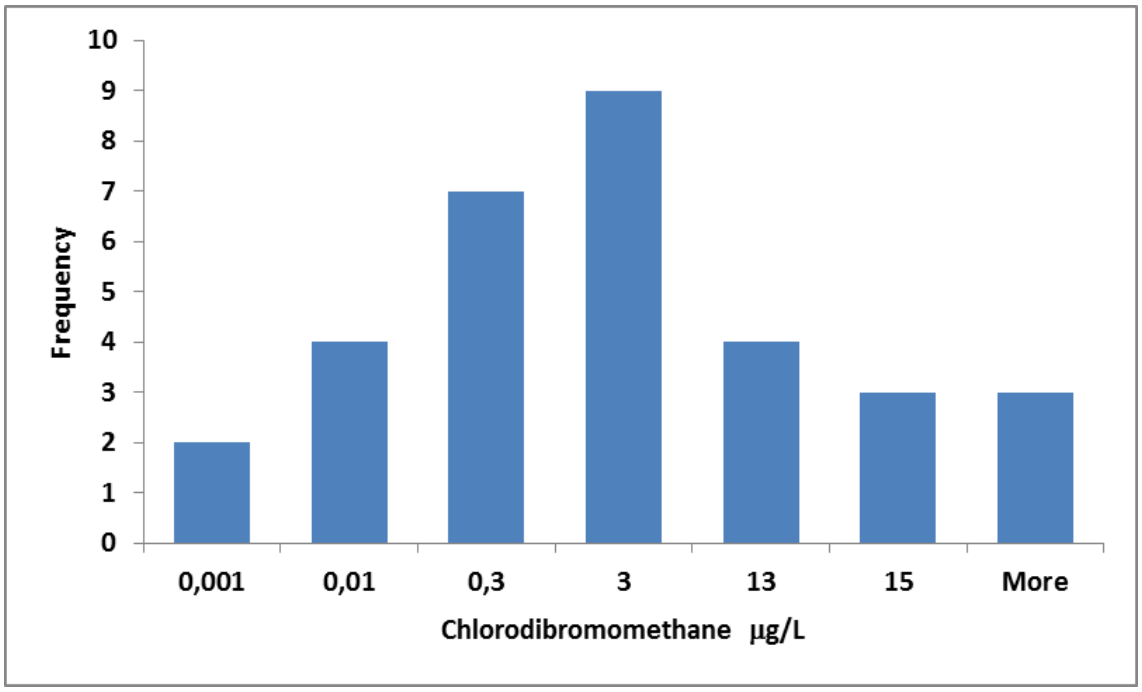

Figure 4.3. Distrubution of Chlorodibromomethane Concentrations

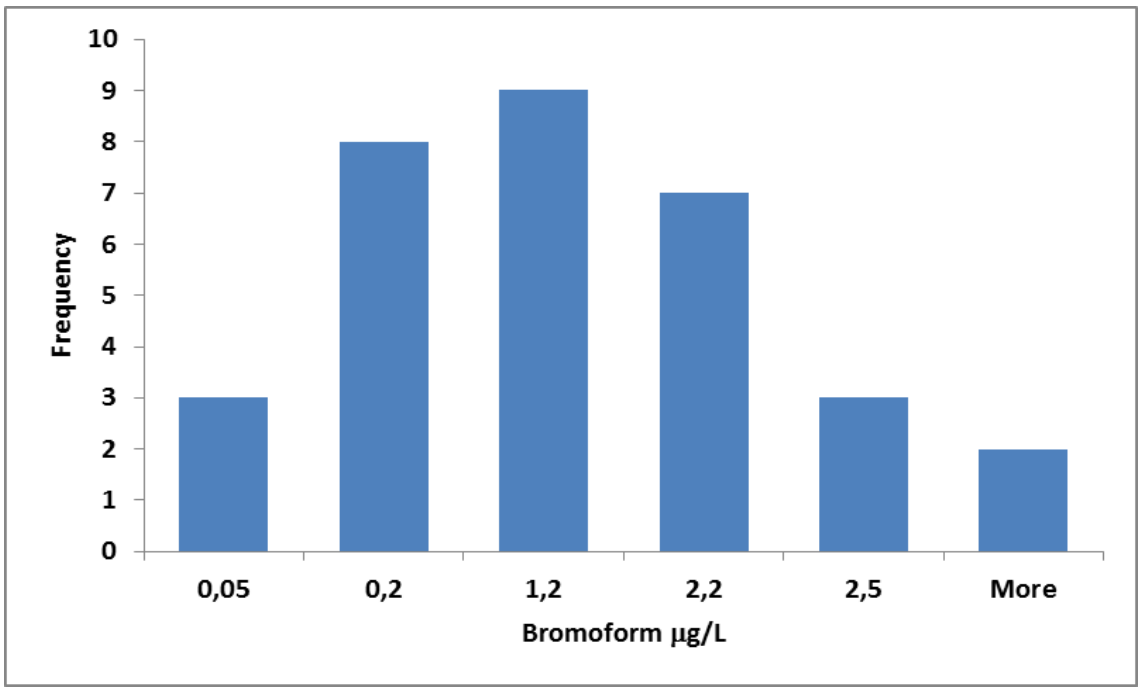

Figure 4.4. Distrubution of Bromoform Concentrations

4.2. Exposure Data

For each route, exposure pathways considered in this study, are shown in Table 4.4. Time-activity data related to these pathways are presented in Table 4.5. Drinking water intake rate data are presented in Table 4.6.

Table 4.4. Routes and Pathways Considered in this Study

Route / Pathway	**Ingestion**	**Inhalation**	**Dermal**
Drinking Water (L/day)	●	-	-
Hand Wash (min)	-	●	●
Dish Washing (min)	-	●	●
Showering (min)	-	●	●
Bath (min)	-	●	●

Table 4.5. Descriptive Statistics for Time-Activity Data

	Median	Mean	SD	Min	Max	95th percentile
Hand Wash (min)	9	10.9	5.5	4	31	21.8
Dish Washing (min)	20	30.1	54.4	0	309	52.8
Showering (min)	18	20.3	9.7	0	54	34.4
Bath (min)	0	16.7	24.2	0	110	47.4

Table 4.6. Descriptive Statistics for Drinking Water Intake Rates

	Median	Mean	SD	Min	Max	95th percentile
Intake Rates (L/day)	1,4	1,6	0,9	0,4	4,5	31.2

4.3. Risk Factors

Values of the risk factors used in this study were obtained from the Integrated Risk Information System (IRIS), and are given in Table 4.7.

Table 4.7. Risk Factor Values
(Source: IRIS, 2005)

DBP	**Slope Facor (SF) per(mg/kg)/day**	**RPF= $SF_i/SF_{index\ chemical}$**	**Drinking Water Unit Risk per (μg/L)**	**Inhalation Unit Risk per (μg/m3)**
Genotoxic Subclass				
Bromodichloromethane (BDCM)	6.2 x10^{-2}	=0.062/0.062 =1	1.8 x10^{-6}	-
Dibromochloromethane (DBCM)	8.4 x10^{-2}	=0.084/0.062 =1.355	2.4 x10^{-6}	-
Bromoform ($CHBr_3$)	7.9 x10^{-3}	=0.0079/0.062 =0.127	2.3x10^{-7}	1.1 x10^{-6}
Non-Genotoxic				
Chloroform ($CHCl_3$)	RfD:0.01 (mg/kg/day)	-	-	2.3 x10^{-5}

4.4. Exposure Assessment

In the calculation, five exposure scenarios were considered. These are;

- **Minimum Exposure Scenario:** Minimum values of each input variable that would minimize the model output (exposure-risk) value are considered.
- **Lower Bound Scenario:** 5th percentile values of each input variable are used
- **Central Tendency Scenario:** The median value of each input variable to calculate a 50th percentile exposure-risk value.

- **Central Tendency Scenario:** The median value of each input variable to calculate a 50^{th} percentile exposure-risk value.
- **Upper Bound Scenario:** 95^{th} percentile values of each input variable are used.
- **Maximum Exposure Scenario:** Maximum values of each input variable that would maximize the model output (exposure-risk) value are considered.

4.5. Exposure Factor

Exposure factor can be calculated as fallows (ATSDR, 2005):

$$EF = \frac{FxED}{AT} \tag{4.1}$$

where,

EF = Exposure factor (unitless)

F = Frequency of exposure (days/year)

ED = Exposure duration (years)

AT = Averaging time for non-carcinogenic subtances (EDx365 days/years)

AT = Averaging time for carcinogenic subtances (LTx365 days/years)

LT =Life time (years)

4.6. Exposure Dose Calculation

The calculation of exposure dose depends on pathway of exposure. Therefore there are three kinds of exposure dose equation.

4.6.1. Water Ingestion Exposure Dose Calculation

Exposure dose because of ingestion can be calculated as (ATSDR, 2005);

$$D = \frac{CxIRxEF}{BW} \tag{4.2}$$

where,

D = Exposure dose (mg/kg/day)

C = Contaminant concentration (mg/L)

IR = Intake rate (L/day)

EF = Exposure factor (unitless)

BW = Body weight (kg)

4.6.2. Air Inhalation Exposure Dose Calculation

Exposure dose from inhalation of air can be calculated as (ATSDR, 2005);

$$D = \frac{CxIRxEF}{BW} \tag{4.3}$$

where,

D = Exposure dose (mg/kg/day)

C = Contaminant concentration (mg/m^3)

IR = Intake rate (m^3/day)

EF = Exposure factor (unitless)

BW = Body weight (kg)

4.6.2.1. Transfer Efficiency Calculation

THMs present in water are ultimately transferred to air as a result of their volatility. The transfer efficiencies were determined experimentally by measurements of the chemical content of water entering and leaving the exposure area during activities (McKone, 1987). Chloroform is chosen as a base chemical because it is the most studied THM. Transfer efficiency to air from shower, from bathroom and from house for chloroform was reported as 0.65 (unitless) (Williams et al., 2002). The transfer efficiency of THMs other than chloroform is calculated under the assumption that the transfer efficiency is in proportion to overall mass-transfer coefficient K at the liquid gas boundary (McKone, 1987).

$$\Phi_i^{\,j} = \Phi_i^{\,Ch} \times \frac{K(j)}{K(Ch)} = \Phi_i^{\,Ch} \frac{\left(\frac{2.5}{D_l^{\,2/3}} + \frac{RT}{D_a^{\,2/3} H}\right)_{Ch}}{\left(\frac{2.5}{D_l^{\,2/3}} + \frac{RT}{D_a^{\,2/3} H}\right)_j} \qquad (4.4)$$

(Source: McKone, 1987)

$\Phi_i^{\,j}$ = transfer efficiency for species j for water use in compartment ***i,*** unitless

$\Phi_i^{\,Ch}$ = transfer efficiency for chloroform as derived from measurements for water use, in compartment i, 0.65 unitless.

K = overall mass-transfer coefficient, m/s

R = gas constant, 0.00008205 L. atm/mo1.K

T = temperature, K

H = Henry's law constant,

D_1 = the diffusion coefficient of the chemical in water, m^2/s;

D_a = the diffusion coefficient of the chemical in air, m^2/s;

4.6.3. Water Dermal Contact Exposure Dose Calculation

Exposure dose from dermal contact of water can be calculated as (ATSDR, 2005);

$$D = \frac{CxKpsxSAxETxCF}{BW} \qquad (4.5)$$

where,

D = Dose (mg/kg/day)

C = Contaminant concentration (mg/m^3)

K_ps = Permeability coefficient (cm/hr)

SA = Exposed body surface area (cm^2)

ET = Exposure time (hours/day)

CF = Conversion factor (1L/1000 cm^3)

BW = Body weight (kg)

4.6.3.1. Body Surface Area

To calculate dermal exposure dose, body surface area is a parameter calculated. The improved equation is to predict body surface area from a patient's weight. Body surface area is calculated using the following equation (Edward et al., 2001).

$$BSA = a \times BW^{b} \quad (4.6)$$

where;

BSA = Body surface area,

a = Dimensionless coefficient, (0.1173)

BW = Body weight in kilograms,

b = Dimensionless scaling coefficient. (0.6466)

4.7. Risk Assessment

Non-carcinogenic risk is calculated using the following equation (USEPA 1999b);

$$HQ = \frac{CDI}{RfD} \quad (4.7)$$

Hazard index (HI) is the sum of the HQ values for each of the mixture components (Eq. 4.9). When HQ or HI value for a mixture exceeds 1, it represents a concern of health risk (Krishnan et al., 1997). The hazard index does not define dose-response relationships, and its numerical value should not be constructed to be a direct estimate of risk (USEPA 1986).

$$HI = \sum_{1}^{N} HQ_n \quad (4.8)$$

HI: Hazard Index

HQ: Hazard Quotient

CDI: Chronic Daily Intake (mg/kg/d)

RfD: Reference Dose (mg/kg/d)

Carcinogenic risk is calculated using the following equation (USEPA 1999a);

$$R = CDI \times SF \tag{4.9}$$

R: Risk

SF: Slope Factor $(mg/kg/d)^{-1}$

CDI: Chronic Daily Intake (mg/kg/d)

According to ICED approach, risk is calculated using the following equation;

Subclass Risk= MLE Slope Factor × Subclass ICED

Total Mixture Risk= Subclass $Risk_1$ + Subclass $Risk_2$ + … + Subclass $Risk_n$

CHAPTER 5

RESULTS

The processes of risk assessment include data collection, data evaluation, exposure assessment, toxicity assessment and risk characterization. Cancer risk assessment associated with exposure to THMs in drinking water through ingestion, inhalation and dermal exposure route was carried out for Izmir. As previously described, the calculation of risk was based on two methods: simple addition and ICED. Results of the assessment are presented in this chapter following with Discussions (Chapter 6).

5.1. Results of the Exposure Factors' Calculation

The exposure factors were identified by determining of magnitude, duration, and frequency of exposure to the contaminants. There are some assumptions for calculation of exposure factor. These are;

- Frequency of exposure of water by drinking water: 365 days/year
- Exposure duration is equal to life time: 70 year male or female
- Averaging time for carcinogenic substances is equal to life time: 70 years.

Based on these assumptions the calculated exposure factor values are all unity for all five scenarios (Table 5.1).

Table 5.1. Calculated Exposure Factor Values

	Frequency of Exposure (days/year)	Exposure Duration (years)	Averaging time for Carcinogenic Substances: BDCM, DBCM, Bromoform (Life time 70 year x 365days/year)	Averaging time for Non-Carcinogenic Substances: Choloform (Exposure Duration year x 365days/year)	Exposure Factor - For Carcinogenic Substances	Exposure Factor- For Non-Carcinogenic Substances
Smallest Exposure Scenario	365	70	25550	25550	1	1
Lower Bond Scenario (%5)	365	70	25550	25550	1	1
Central Tendency (%50)	365	70	25550	25550	1	1
Upper Bond Scenario (%95)	365	70	25550	25550	1	1
Max Exposure Scenario	365	70	25550	25550	1	1

5.2. Results of the Exposure Dose by Water Ingestion

Exposure dose (chronic daily intake, CDI) was implemented on THMs component based, incorporating parameters for chemical concentrations in the water supply, intake rate and human physical characteristics.

Calculated values of CDI are presented in Tables 5.2, 5.3, 5.4, and 5.5 for chloroform, BDCM, DBCM, and bromoform, respectively. Considerations about the calculations are as follows.

- Concentrations and intake rate of a compound is calculated by interpolation for different scenarios such as lower bound, central tendency.
- Body weight is also calculated by interpolation. But a negative correlation exists between body weight and exposure dose. When the body weight increase, exposure dose decreases.

Table 5.2. Ingestion Dose for Chloroform

	Concentration of chloroform (mg/l)	Intake rate (L/day)	Exposure Factor-For non-carcinogenic substances	Body Weight (kg)	Ingestion Dose For non-carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.84×10^{-14}	0.3666	1	96	1.47×10^{-16}
Lower Bound Exposure Scenario	8.10×10^{-11}	0.40368	1	92.4	3.54×10^{-13}
Central Tendency Exposure Scenario	9.00×10^{-5}	1.4284	1	67	1.92×10^{-6}
Upper Bound Exposure Scenario	2.99×10^{-2}	3.11992	1	47,6	1.96×10^{-3}
Maximum Exposure Scenario	3.46×10^{-2}	4.4856	1	47	3.30×10^{-3}

Table 5.3. Ingestion Dose for Bromodichloromethane

	Concentration of BDCM (mg/l)	Intake rate (L/day)	Exposure Factor-For non-carcinogenic substances	Body Weight (kg)	Ingestion Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	4.76×10^{-9}	0.3666	1	96	1.82×10^{-11}
Lower Bound Exposure Scenario	7.40×10^{-7}	0.40368	1	92.4	3.23×10^{-9}
Central Tendency Exposure Scenario	1.20×10^{-4}	1.4284	1	67	2.56×10^{-6}
Upper Bound Exposure Scenario	2.46×10^{-2}	3.11992	1	47.6	1.61×10^{-3}
Maximum Exposure Scenario	2.75×10^{-2}	4.4856	1	47	2.62×10^{-3}

Table 5.4. Ingestion Dose for Dibromochloromethane

	Concentration of DBCM (mg/l)	Intake rate (L/day)	Exposure Factor-For non-carcinogenic substances	Body Weight (kg)	Ingestion Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.24×10^{-7}	0.3666	1	96	1.24×10^{-9}
Lower Bound Exposure Scenario	7.03×10^{-7}	0.40368	1	92.4	3.07×10^{-9}
Central Tendency Exposure Scenario	4.10×10^{-4}	1.4284	1	67	8.74×10^{-6}
Upper Bound Exposure Scenario	1.53×10^{-2}	3.11992	1	47.6	1.00×10^{-3}
Maximum Exposure Scenario	1.72×10^{-2}	4.4856	1	47	1.64×10^{-3}

Table 5.5. Ingestion Dose for Bromoform

	Concentration of bromoform (mg/l)	Intake rate (L/day)	Exposure Factor-For non-carcinogenic substances	Body Weight (kg)	Ingestion Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.97×10^{-6}	0.3666	1	96	1.52×10^{-8}
Lower Bound Exposure Scenario	1.40×10^{-5}	0.40368	1	92.4	6.12×10^{-8}
Central Tendency Exposure Scenario	4.50×10^{-4}	1.4284	1	67	9.59×10^{-6}
Upper Bound Exposure Scenario	2.52×10^{-3}	3.11992	1	47.6	1.65×10^{-4}
Maximum Exposure Scenario	3.22×10^{-3}	4.4856	1	47	3.07×10^{-4}

5.3. Results of the Exposure Dose by Air Inhalation

On the inhalation pathway, to determine the exposure dose, the effects of parameters are important. The results indicate that the pathway dose factor is most sensitive to changes in the uptake fraction in the lung, the ratio of breathing rate to body weight, the water to air transfer efficiency and the quantity of water used in showers. The exposure dose results are based on THMs component such as chloroform, dibromochloromethane, bromodichloromethane and bromoform. Considerations about the calculations are as follows.

- Air intake rate is different for men and women. 11.3 m^3/day female 19-65 years; 15.2 m^3/day male 19-65 years (USEPA 1997). While establishing the scenarios, age and gender parameter is considered for the calculation of air intake rate. Intake rate of a compound is calculated by interpolation for different scenarios such as lower bound, central tendency.
- Body weight is also calculated by interpolation. But a negative correlation exists between body weight and exposure dose. When the body weight increase, exposure dose decreases.
- Transfer efficiency is an important factor to calculate the THMs concentrations from water to air. Assumed temperature values for different exposure related activities are given in Table 5.6. Calculated transfer efficiencies follow in Table 5.7.

Table 5.6. Estimated Temperature for Activities
(Source: Wilkes et al., 2002)

Activity	**Temperature ˚C**
Showering	40
Bathing and Dish Washing	35
Hand washing	25

Table 5.7. Calculated Transfer Efficiencies

Appliance	**Transfer Efficiency (Unitless)**		
	BDCM	**DBCM**	**Bromoform**
Showering	0.4116	0.1716	0.1063
Bathing	0.3961	0.1682	0.0988
Hand wash	0.3808	0.1582	0.0884
Dish wash	0.3961	0.1682	0.0988

- THMs concentrations in air were calculated with the following equation.

$$C_{THM} = (C_{Chemical} \times R_{Water} \times \Phi_i^j \times ET) / R_{Air} \quad (5.1)$$

where,

C_{THM} = THMs concentrations in air ($\mu g/m^3$)

$C_{Chemical}$ = Concentration of a chemical in water ($\mu g/L$)

R_{Water} = Water use rate during the activity (L/h)

Φ_i^j = Transfer efficiency from water to air (unitless)

ET = Exposure time (min/day)

R_{Air} = Air exchange rate during the activity (m^3/h)

- Aggregate exposure for hand washing, shower, bath, dish washing activities was considered. Calculated CDI values are presented in Tables 5.8, 5.9, 5.10, and 5.11 for chloroform, BDCM, DBCM, and bromoform, respectively.

Table 5.8. Inhalation Dose for Chloroform

	Concentration of chloroform (mg/m^3)	Inhalation rate (m^3/day)	Exposure Factor- For non-carcinogenic substances	Body Weight (kg)	Inhalation Dose For non-carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	4.88×10^{-15}	11.3	1	96	5.75×10^{-16}
Lower Bound Exposure Scenario	1.74×10^{-11}	11.3	1	92.4	2.13×10^{-12}
Central Tendency Exposure Scenario	4.74×10^{-4}	11.3	1	67	7.99×10^{-5}
Upper Bound Exposure Scenario	3.35×10^{-1}	15.2	1	47.6	1.07×10^{-1}
Maximum Exposure Scenario	5.17×10^{-1}	15.2	1	47	1.67×10^{-1}

Table 5.9. Inhalation Dose for Bromodichloromethane

	Concentration of BDCM (mg/m^3)	Inhalation rate (m^3/day)	Exposure Factor- For carcinogenic substances	Body Weight (kg)	Inhalation Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	5.95×10^{-10}	11.3	1	96	7.00×10^{-11}
Lower Bound Exposure Scenario	1.37×10^{-7}	11.3	1	92.4	1.67×10^{-8}
Central Tendency Exposure Scenario	5.17×10^{-4}	11.3	1	67	8.72×10^{-5}
Upper Bound Exposure Scenario	1.44×10^{-1}	15.2	1	47.6	4.59×10^{-2}
Maximum Exposure Scenario	2.58×10^{-1}	15.2	1	47	8.35×10^{-2}

Table 5.10. Inhalation Dose for Dibromochloromethane

	Concentration of DBCM (mg/m^3)	Inhalation rate (m^3/day)	Exposure Factor- For carcinogenic substances	Body Weight (kg)	Inhalation Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	2.39×10^{-8}	11.3	1	96	2.82×10^{-9}
Lower Bound Exposure Scenario	4.13×10^{-7}	11.3	1	92.4	5.05×10^{-8}
Central Tendency Exposure Scenario	8.97×10^{-4}	11.3	1	67	1.51×10^{-4}
Upper Bound Exposure Scenario	4.04×10^{-2}	15.2	1	47.6	1.29×10^{-2}
Maximum Exposure Scenario	6.80×10^{-2}	15.2	1	47	2.20×10^{-2}

Table 5.11. Inhalation Dose for Bromoform

	Concentration of bromoform (mg/m^3)	Inhalation rate (m^3/day)	Exposure Factor-For carcinogenic substances	Body Weight (kg)	Inhalation Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	1.64×10^{-7}	11.3	1	96	1.93×10^{-8}
Lower Bound Exposure Scenario	3.14×10^{-6}	11.3	1	92.4	3.84×10^{-7}
Central Tendency Exposure Scenario	6.48×10^{-4}	11.3	1	67	1.09×10^{-4}
Upper Bound Exposure Scenario	4.28×10^{-3}	15.2	1	47.6	1.37×10^{-3}
Maximum Exposure Scenario	5.83×10^{-3}	15.2	1	47	1.89×10^{-3}

5.4. Results of the Exposure Dose by Water Dermal Contact

The parameters which affect dermal absorption dose are concentration of chemical, permeability coefficient, surface area dermal intake contact, exposure time, and body weight. Permeability coefficient values were obtained from the literature and presented in Table 5.12. Calculated values of CDI are presented in Tables 5.13 to 5.20. Considerations about the calculations are as follows.

Dermal exposure calculations are divided into two groups because of different body surface area depends on activity type. Bath and showering is the first group. Body surface area is classified as the whole body area. The second group is hand and dish washing. Body surface area is classified as hand area.

- Exposure time and concentration are calculated for the first group and the second group separately by interpolation for different scenarios such as lower bound, central tendency.
- Body weight is also calculated by interpolation. But a negative correlation exists between body weight and exposure dose. When the body weight increase, exposure dose decreases.
- Body surface area is calculated according to equation (4.6) . Surface area in cm^2 for hands is %4 of total body surface area (Edward et al., 2001).
- Permeability coefficient, for the outermost layer of the skin, is a measure of a contaminant's capacity to permeate through it. In dermal exposure permeability coefficient, in cm/hr, depends on type of chemical.

Table 5.12. Permeability Coefficients (K_ps) For Some Chemicals
(Source: US EPA, 2003)

Chemical Name	**K_p(cm/hr)**
Chloroform	8.90×10^{-3}
Bromoform	2.60×10^{-3}
Bromodichloromethane	5.80×10^{-3}
Chlorodibromomethane	3.90×10^{-3}

Table 5.13. Dermal Dose for Chloroform During Bath and Shower

	Concentration of chloroform (mg/l)	Permeability coefficient (cm/hr)	Exposed body surface area (cm^2)	Exposure Time (h/day)	Conversion Factor (1L/ $1000cm^3$)	Body Weight (kg)	Dermal Dose For non-carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.84×10^{-14}	0.0089	14141	1.83×10^{-1}	0.001	96	9.23×10^{-18}
Lower Bound Exposure Scenario	8.10×10^{-11}	0.0089	14257	1.83×10^{-1}	0.001	92.4	2.04×10^{-14}
Central Tendency Exposure Scenario	9.00×10^{-5}	0.0089	17784	4.45×10^{-1}	0.001	67	9.45×10^{-8}
Upper Bound Exposure Scenario	2.99×10^{-2}	0.0089	21893	1.23	0.001	47.6	1.51×10^{-4}
Maximum Exposure Scenario	3.46×10^{-2}	0.0089	22441	2.33	0.001	47	3.43×10^{-4}

Table 5.14. Dermal Dose for Bromodichloromethane During Bath and Shower

	Concentration of BDCM (mg/l)	Permeability coefficient (cm/hr)	Exposed body surface area (cm^2)	Exposure Time (h/day)	Conversion Factor (1L/ $1000cm^3$)	Body Weight (kg)	Dermal Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	4.76×10^{-9}	0.0058	14141	1.83×10^{-1}	0.001	96	7.46×10^{-13}
Lower Bound Exposure Scenario	7.40×10^{-7}	0.0058	14257	1.83×10^{-1}	0.001	92.4	1.21×10^{-10}
Central Tendency Exposure Scenario	1.20×10^{-4}	0.0058	17784	4.45×10^{-1}	0.001	67	8.21×10^{-8}
Upper Bound Exposure Scenario	2.46×10^{-2}	0.0058	21893	1.23	0.001	47.6	8.09×10^{-5}
Maximum Exposure Scenario	2.75×10^{-2}	0.0058	22441	2.33	0.001	47	1.78×10^{-4}

Table 5.15. Dermal Dose for Dibromochloromethane During Bath and Shower

	Concentration of DBCM (mg/l)	Permeability coefficient (cm/hr)	Exposed body surface area (cm^2)	Exposure Time (h/day)	Conversion Factor (1L/ $1000cm^3$)	Body Weight (kg)	Dermal Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.24×10^{-7}	0.0039	14141	1.83×10^{-1}	0.001	96	3.41×10^{-11}
Lower Bound Exposure Scenario	7.03×10^{-7}	0.0039	14257	1.83×10^{-1}	0.001	92.4	7.76×10^{-11}
Central Tendency Exposure Scenario	4.10×10^{-4}	0.0039	17784	4.45×10^{-1}	0.001	67	189×10^{-7}
Upper Bound Exposure Scenario	1.53×10^{-2}	0.0039	21893	1.23	0.001	47.6	3.38×10^{-5}
Maximum Exposure Scenario	1.72×10^{-2}	0.0039	22441	2.33	0.001	47	7.47×10^{-5}

Table 5.16. Dermal Dose for Bromoform During Bath and Shower

	Concentration of bromoform (mg/l)	Permeability coefficient (cm/hr)	Exposed body surface area (cm^2)	Exposure Time (h/day)	Conversion Factor (1L/ $1000cm^3$)	Body Weight (kg)	Dermal Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.97×10^{-6}	0.0026	14141	1.83×10^{-1}	0.001	96	2.79×10^{-10}
Lower Bound Exposure Scenario	1.40×10^{-5}	0.0026	14257	1.83×10^{-1}	0.001	92.4	1.03×10^{-9}
Central Tendency Exposure Scenario	4.50×10^{-4}	0.0026	17784	4.45×10^{-1}	0.001	67	1.38×10^{-7}
Upper Bound Exposure Scenario	2.52×10^{-3}	0.0026	21893	1.23	0.001	47.6	3.71×10^{-6}
Maximum Exposure Scenario	3.22×10^{-3}	0.0026	22441	2.33	0.001	47	9.33×10^{-6}

Table 5.17. Dermal Dose for Chloroform During Dish and Hand Wash

	Concentration of chloroform (mg/l)	Permeability coefficient (cm/hr)	Exposed body surface area (cm^2)	Exposure Time (h/day)	Conversion Factor (1L/ $1000cm^3$)	Body Weight (kg)	Dermal Dose For non-carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.84×10^{-14}	0.0089	14141	1.83×10^{-1}	0.001	96	1.49×10^{-19}
Lower Bound Exposure Scenario	8.10×10^{-11}	0.0089	14257	1.83×10^{-1}	0.001	92.4	4.24×10^{-16}
Central Tendency Exposure Scenario	9.00×10^{-5}	0.0089	17784	4.45×10^{-1}	0.001	67	4.14×10^{-9}
Upper Bound Exposure Scenario	2.99×10^{-2}	0.0089	21893	1.23	0.001	47.6	5.61×10^{-6}
Maximum Exposure Scenario	3.46×10^{-2}	0.0089	22441	2.33	0.001	47	3.33×10^{-5}

Table 5.18. Dermal Dose for Bromodichloromethane During Dish and Hand Wash

	Concentration of BDCM (mg/l)	Permeability coefficient (cm/hr)	Exposed body surface area (cm^2)	Exposure Time (h/day)	Conversion Factor (1L/ $1000cm^3$)	Body Weight (kg)	Dermal Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	4.76×10^{-9}	0.0058	14141	1.83×10^{-1}	0.001	96	1.20×10^{-14}
Lower Bound Exposure Scenario	7.40×10^{-7}	0.0058	14257	1.83×10^{-1}	0.001	92.4	2.52×10^{-12}
Central Tendency Exposure Scenario	1.20×10^{-4}	0.0058	17784	4.45×10^{-1}	0.001	67	3.60×10^{-9}
Upper Bound Exposure Scenario	2.46×10^{-2}	0.0058	21893	1.23	0.001	47.6	3.01×10^{-6}
Maximum Exposure Scenario	2.75×10^{-2}	0.0058	22441	2.33	0.001	47	1.72×10^{-5}

Table 5.19. Dermal Dose for Dibromochloromethane During Dish and Hand Wash

	Concentration of DBCM (mg/l)	Permeability coefficient (cm/hr)	Exposed body surface area (cm^2)	Exposure Time (h/day)	Conversion Factor (1L/ $1000cm^3$)	Body Weight (kg)	Dermal Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.24×10^{-7}	0.0039	14141	1.83×10^{-1}	0.001	96	5.49×10^{-13}
Lower Bound Exposure Scenario	7.03×10^{-7}	0.0039	14257	1.83×10^{-1}	0.001	92.4	1.61×10^{-12}
Central Tendency Exposure Scenario	4.10×10^{-4}	0.0039	17784	4.45×10^{-1}	0.001	67	8.27×10^{-9}
Upper Bound Exposure Scenario	1.53×10^{-2}	0.0039	21893	1.23	0.001	47.6	1.26×10^{-6}
Maximum Exposure Scenario	1.72×10^{-2}	0.0039	22441	2.33	0.001	47	7.24×10^{-6}

Table 5.20. Dermal Dose for Bromoform During Dish and Hand Wash

	Concentration of bromoform (mg/l)	Permeability coefficient (cm/hr)	Exposed body surface area (cm^2)	Exposure Time (h/day)	Conversion Factor (1L/ $1000cm^3$)	Body Weight (kg)	Dermal Dose For carcinogenic substances (mg /kg/day)
Minimum Exposure Scenario	3.97×10^{-6}	0.0026	14141	1.83×10^{-1}	0.001	96	4.49×10^{-12}
Lower Bound Exposure Scenario	1.40×10^{-5}	0.0026	14257	1.83×10^{-1}	0.001	92.4	2.14×10^{-11}
Central Tendency Exposure Scenario	4.50×10^{-4}	0.0026	17784	4.45×10^{-1}	0.001	67	6.05×10^{-9}
Upper Bound Exposure Scenario	2.52×10^{-3}	0.0026	21893	1.23	0.001	47.6	1.38×10^{-7}
Maximum Exposure Scenario	3.22×10^{-3}	0.0026	22441	2.33	0.001	47	9.04×10^{-7}

5.5. Risk Results for Water Ingestion

Quantifying the risk is important for population and decision making policy for drinking water safety. The human risk assessment was conducted to evaluate carcinogenic risk from exposure to THMs in drinking water. The following tables present the estimated risk levels associated with ingestion of THMs in drinking water. Choloroform was considered as noncarcinogenic and carcinogenic substance. Therefore, both hazard quotient and risk calculated. Carcinogenic risk of choloroform for ingestion is calculated by using slope factor as 6.1×10^{-3} (RAIS, 2009). For bromodichloromethane, dibromochloromethane and bromoform, the risk was implemented by two different methods as simple addition and ICED.

Table 5.21. Ingestion Risk for Chloroform

	Chronic-Toxic Risk Hazard Quotient	Carcinogenic Risk
Minimum Exposure Scenario	1.47×10^{-14}	8.95×10^{-19}
Lower Bound Exposure Scenario	3.54×10^{-11}	2.16×10^{-15}
Central Tendency Exposure Scenario	1.92×10^{-4}	$1.17\times10\text{-}^{8}$
Upper Bound Exposure Scenario	1.96×10^{-1}	1.20×10^{-5}
Maximum Exposure Scenario	3.30×10^{-1}	2.01×10^{-5}

Table 5.22. Ingestion Risk for Bromodichloromethane

	Carcinogenic Risk	RPF= SF_{BDCM}/SF_{BDCM}	Component ICED for BDCM
Minimum Exposure Scenario	1.13×10^{-12}	1.00	1.82×10^{-11}
Lower Bound Exposure Scenario	2.00×10^{-10}	1.00	3.23×10^{-9}
Central Tendency Exposure Scenario	1.59×10^{-7}	1.00	2.56×10^{-6}
Upper Bound Exposure Scenario	1.00×10^{-4}	1.00	1.61×10^{-3}
Maximum Exposure Scenario	1.63×10^{-4}	1.00	2.62×10^{-3}

Table 5.23. Ingestion Risk for Dibromochloromethane

	Carcinogenic Risk	RPF= SF_{DBCM}/SF_{BDCM}	Component ICED for DBCM
Minimum Exposure Scenario	1.04×10^{-10}	1.354839	1.68×10^{-9}
Lower Bound Exposure Scenario	2.58×10^{-10}	1.354839	4.16×10^{-9}
Central Tendency Exposure Scenario	7.34×10^{-7}	1.354839	1.18×10^{-5}
Upper Bound Exposure Scenario	8.42×10^{-5}	1.354839	1.36×10^{-3}
Maximum Exposure Scenario	1.38×10^{-4}	1.354839	2.22×10^{-3}

Table 5.24. Ingestion Risk for Bromoform

	Carcinogenic Risk	RPF= SF_{CHBr3}/SF_{BDCM}	Component ICED for Bromoform
Minimum Exposure Scenario	1.19767×10^{-10}	0.127419	1.93×10^{-9}
Lower Bound Exposure Scenario	4.83469×10^{-10}	0.127419	7.80×10^{-9}
Central Tendency Exposure Scenario	7.57905×10^{-8}	0.127419	1.22×10^{-6}
Upper Bound Exposure Scenario	1.30279×10^{-6}	0.127419	2.10×10^{-5}
Maximum Exposure Scenario	2.42776×10^{-6}	0.127419	3.91×10^{-5}

5.6. Risk Results for Air Inhalation

Inhalation risk values were estimated by THM exposures in showering, bathing, and dish and hand washing. Risk values, by two different methods, for carcinogenic THMs species are present in below tables. For chloroform, hazard quotient and risk are available. Carcinogenic risk of choloroform for inhalation is calculated by using slope factor as 8.1×10^{-2} (RAIS, 2009).

Table 5.25. Inhalation Risk for Chloroform

	Hazard Quotient For Non-Carcinogenic Substances	Risk For Carcinogenic Substances
Minimum Exposure Scenario	5.75×10^{-14}	4.65×10^{-17}
Lower Bound Exposure Scenario	2.13×10^{-10}	1.72×10^{-13}
Central Tendency Exposure Scenario	7.99×10^{-3}	6.47×10^{-6}
Upper Bound Exposure Scenario	1.07×10^{1}	8.68×10^{-3}
Maximum Exposure Scenario	1.67×10^{1}	1.35×10^{-2}

Table 5.26. Inhalation Risk for Bromodichloromethane

	Carcinogenic Risk	RPF= SF_{BDCM}/SF_{BDCM}	Component ICED for BDCM
Minimum Exposure Scenario	4.34×10^{-12}	1.00	7.00×10^{-11}
Lower Bound Exposure Scenario	1.04×10^{-9}	1.00	1.67×10^{-8}
Central Tendency Exposure Scenario	5.40×10^{-6}	1.00	8.72×10^{-5}
Upper Bound Exposure Scenario	2.85×10^{-3}	1.00	4.59×10^{-2}
Maximum Exposure Scenario	5.18×10^{-3}	1.00	8.35×10^{-2}

Table 5.27. Inhalation Risk for Dibromochloromethane

	Carcinogenic Risk	RPF= SF_{DBCM}/SF_{BDCM}	Component ICED for DBCM
Minimum Exposure Scenario	2.37×10^{-10}	1.354839	3.82×10^{-9}
Lower Bound Exposure Scenario	4.24×10^{-9}	1.354839	6.84×10^{-8}
Central Tendency Exposure Scenario	1.27×10^{-5}	1.354839	2.05×10^{-4}
Upper Bound Exposure Scenario	1.08×10^{-3}	1.354839	1.75×10^{-2}
Maximum Exposure Scenario	1.85×10^{-3}	1.354839	2.98×10^{-2}

Table 5.28. Inhalation Risk for Bromoform

	Carcinogenic Risk	RPF= SF_{CHBr3}/SF_{BDCM}	Component ICED for Bromoform
Minimum Exposure Scenario	1.52×10^{-10}	0.127419	2.46×10^{-9}
Lower Bound Exposure Scenario	3.03×10^{-9}	0.127419	4.89×10^{-8}
Central Tendency Exposure Scenario	8.64×10^{-7}	0.127419	1.39×10^{-5}
Upper Bound Exposure Scenario	1.08×10^{-5}	0.127419	1.74×10^{-4}
Maximum Exposure Scenario	$1.49\text{x}10^{-5}$	0.127419	$2.40\text{x}10^{-4}$

5.7. Risk Results for Water Dermal Contact

Dermal risk estimation divided into two groups because of different activities and exposure doses. One group risk is result of bathing and showering activities; the other group is hand and dish washing. Carcinogenic and noncarcinogenic risks were associated with the species of THMs. For chloroform, hazard quotient and risk are available. Carcinogenic risk of choloroform for dermal route is calculated by using slope factor as 6.1×10^{-3} (Lee et al., 2009).

Tables 5.29-5.32 present dermal absorption risks associated with bathing and showering activities, Tables 5.33-5.36 present dermal absorption risks associated with hand and dish washing.

Table 5.29. Bathing and Showering Dermal Risk for Chloroform

	Hazard Quotient For Non-Carcinogenic Substances	Risk For Carcinogenic Substances???
Minimum Exposure Scenario	9.23×10^{-16}	5.63×10^{-20}
Lower Bound Exposure Scenario	2.04×10^{-12}	1.24×10^{-16}
Central Tendency Exposure Scenario	9.45×10^{-6}	5.76×10^{-10}
Upper Bound Exposure Scenario	1.51×10^{-2}	9.21×10^{-7}
Maximum Exposure Scenario	3.43×10^{-2}	2.09×10^{-6}

Table 5.30. Bathing and Showering Dermal Risk for Bromodichloromethane

	Carcinogenic Risk	RPF= SF_{BDCM}/SF_{BDCM}	Component ICED for BDCM
Minimum Exposure Scenario	4.62×10^{-14}	1.000000	7.46×10^{-13}
Lower Bound Exposure Scenario	7.53×10^{-12}	1.000000	1.21×10^{-10}
Central Tendency Exposure Scenario	5.09×10^{-9}	1.000000	8.21×10^{-8}
Upper Bound Exposure Scenario	5.02×10^{-6}	1.000000	8.09×10^{-5}
Maximum Exposure Scenario	1.10×10^{-5}	1.000000	1.78×10^{-4}

Table 5.31. Bathing and Showering Dermal Risk for Dibromochloromethane

	Carcinogenic Risk	RPF= SF_{DBCM}/SF_{BDCM}	Component ICED for DBCM
Minimum Exposure Scenario	2.87×10^{-12}	1.354839	4.62×10^{-11}
Lower Bound Exposure Scenario	6.52×10^{-12}	1.354839	1.05×10^{-10}
Central Tendency Exposure Scenario	1.58×10^{-8}	1.354839	2.56×10^{-7}
Upper Bound Exposure Scenario	2.84×10^{-6}	1.354839	4.59×10^{-5}
Maximum Exposure Scenario	6.28×10^{-6}	1.354839	1.01×10^{-4}

Table 5.32. Bathing and Showering Dermal Risk for Bromoform

	Carcinogenic Risk	RPF= SF_{CHBr3}/SF_{BDCM}	Component ICED for Bromoform
Minimum Exposure Scenario	2.20×10^{-12}	0.127419	3.55×10^{-11}
Lower Bound Exposure Scenario	8.14×10^{-12}	0.127419	1.31×10^{-10}
Central Tendency Exposure Scenario	1.09×10^{-9}	0.127419	1.76×10^{-8}
Upper Bound Exposure Scenario	2.93×10^{-8}	0.127419	4.73×10^{-7}
Maximum Exposure Scenario	7.37×10^{-8}	0.127419	1.19×10^{-6}

Table 5.33. Dish and Hand Washing Dermal Risk for Chloroform

	Hazard Quotient For Non-Carcinogenic Substances	Risk For Carcinogenic Substances
Minimum Exposure Scenario	1.49×10^{-17}	9.07×10^{-22}
Lower Bound Exposure Scenario	4.24×10^{-14}	2.59×10^{-18}
Central Tendency Exposure Scenario	4.14×10^{-7}	2.53×10^{-11}
Upper Bound Exposure Scenario	5.61×10^{-4}	3.43×10^{-8}
Maximum Exposure Scenario	3.33×10^{-3}	2.03×10^{-7}

Table 5.34. Dish and Hand Washing Dermal Risk for Bromodichloromethane

	Carcinogenic Risk	RPF= SF_{BDCM}/SF_{BDCM}	Component ICED for BDCM
Minimum Exposure Scenario	7.44×10^{-16}	1.00	1.20×10^{-14}
Lower Bound Exposure Scenario	1.56×10^{-13}	1.00	2.52×10^{-12}
Central Tendency Exposure Scenario	2.23×10^{-10}	1.00	3.60×10^{-9}
Upper Bound Exposure Scenario	1.87×10^{-7}	1.00	3.01×10^{-6}
Maximum Exposure Scenario	1.07×10^{-6}	1.00	1.72×10^{-5}

Table 5.35. Dish and Hand Washing Dermal Risk for Dibromochloromethane

	Carcinogenic Risk	RFD= SF_{DBCM}/SF_{BDCM}	Component ICED for DBCM
Minimum Exposure Scenario	4.62×10^{-14}	1.354839	7.44×10^{-13}
Lower Bound Exposure Scenario	1.35×10^{-13}	1.354839	2.18×10^{-12}
Central Tendency Exposure Scenario	6.94×10^{-10}	1.354839	1.12×10^{-8}
Upper Bound Exposure Scenario	1.06×10^{-7}	1.354839	1.71×10^{-6}
Maximum Exposure Scenario	6.09×10^{-7}	1.354839	9.82×10^{-6}

Table 5.36. Dish and Hand Washing Dermal Risk for Bromoform

	Carcinogenic Risk	RPF= SF_{CHBr3}/SF_{BDCM}	Component ICED for Bromoform
Minimum Exposure Scenario	3.55×10^{-14}	0.127419	5.71901×10^{-13}
Lower Bound Exposure Scenario	1.69×10^{-13}	0.127419	2.72763×10^{-12}
Central Tendency Exposure Scenario	4.78×10^{-11}	0.127419	7.70698×10^{-10}
Upper Bound Exposure Scenario	1.09×10^{-9}	0.127419	1.75872×10^{-8}
Maximum Exposure Scenario	7.14×10^{-9}	0.127419	1.15206×10^{-7}

5.8. Total Risk

We estimated the multi-pathway exposure risk assessment based on the concentrations of THMs measured in water. Cancer risk caused by exposure through oral ingestion, dermal absorption and inhalation were considered in this study. Cumulative risk was calculated over one route of exposure for the four THMs. Chloroform was contributed to total risk by summing the carcinogenic risk of all the routes. Cumulative risks were brought together to estimate the total risk. Cumulative and total risks are calculated by two methods which are additive method and ICED method.

In ICED approach, MLE slope factors are from the same dose−response model as the 95% upper bound slope factors. Genotoxic subclass index chemical, maximum likelihood estimate (MLE) of cancer slope factor (SF) $=5.7\times10^{-3}$ (Teuschler, 2004). Tables 5.37 to 5.39 present the cumulative risks for the three exposure routes. Table 40 follows with the estimated total risk values.

Table 5.37. Cumulative Risk for Ingestion Route

	ADDITIVE METHOD	**ICED METHOD**	
	Total Carcinogenic Risk	Subclass ICED (mg/kg/d)	Subclass Risk=MLE Slope Factor × Subclass ICED
Minimum Exposure Scenario	2.25×10^{-10}	3.63×10^{-9}	2.07×10^{-11}
Lower Bound Exposure Scenario	9.42×10^{-10}	1.52×10^{-8}	8.66×10^{-11}
Central Tendency Exposure Scenario	9.69×10^{-7}	1.56×10^{-5}	8.91×10^{-8}
Upper Bound Exposure Scenario	1.86×10^{-4}	2.99×10^{-3}	1.71×10^{-5}
Maximum Exposure Scenario	3.03×10^{-4}	4.89×10^{-3}	2.79×10^{-5}

Table 5.38. Cumulative Risk for Inhalation Route

	ADDITIVE METHOD	**ICED METHOD**	
	Total Carcinogenic Risk	Subclass ICED (mg/kg/d)	Subclass Risk=MLE Slope Factor × Subclass ICED
Minimum Exposure Scenario	3.93×10^{-10}	6.34×10^{-9}	3.62×10^{-11}
Lower Bound Exposure Scenario	8.31×10^{-9}	1.34×10^{-7}	7.64×10^{-10}
Central Tendency Exposure Scenario	1.90×10^{-5}	3.06×10^{-4}	1.75×10^{-6}
Upper Bound Exposure Scenario	3.94×10^{-3}	6.36×10^{-2}	3.62×10^{-4}
Maximum Exposure Scenario	7.04×10^{-3}	1.14×10^{-1}	6.47×10^{-4}

Table 5.39. Cumulative Risk for Dermal Route

	ADDITIVE METHOD	**ICED METHOD**	
	Total Carcinogenic Risk	Subclass ICED (mg/kg/d)	Subclass Risk=MLE Slope Factor × Subclass ICED
Minimum Exposure Scenario	5.20×10^{-12}	8.38×10^{-11}	4.78×10^{-13}
Lower Bound Exposure Scenario	2.26×10^{-11}	3.65×10^{-10}	2.08×10^{-12}
Central Tendency Exposure Scenario	2.30×10^{-8}	3.71×10^{-7}	2.11×10^{-9}
Upper Bound Exposure Scenario	8.18×10^{-6}	1.32×10^{-4}	7.52×10^{-7}
Maximum Exposure Scenario	1.91×10^{-5}	3.07×10^{-4}	1.75×10^{-6}

Table 5.40. Estimated Total Carcinogenic Risk

	ADDITIVE METHOD	**ICED METHOD**
	Total Carcinogenic Risk	Subclass Risk=MLE Slope Factor × Subclass ICED
Minimum Exposure Scenario	6.23×10^{-10}	5.73×10^{-11}
Lower Bound Exposure Scenario	9.28×10^{-9}	8.53×10^{-10}
Central Tendency Exposure Scenario	2.00×10^{-5}	1.84×10^{-6}
Upper Bound Exposure Scenario	4.14×10^{-3}	3.80×10^{-4}
Maximum Exposure Scenario	7.36×10^{-3}	6.77×10^{-4}

CHAPTER 6

DISCUSSION

Estimation of cumulative or total human health risks associated with different compounds in a mixture is subject of debate. The cumulative or total risks have been estimated by simply adding risks associated with each compound in the mixture (Legay et al., 2011; Lee et al., 2004; Tokmak et al., 2006; Uyak, 2005). However, the simple addition may result in overestimation of the risks. Therefore, a new cumulative / total risk assessment scheme has recently been proposed (Teuschler et al., 2004). This study estimated cumulative and total carcinogenic risks (by considering all three possible exposure routes) associated with trihalomethanes found in İzmir tap water both through simple addition and the proposed new scheme (Cumulative Relative Potency Factor, CRPF) and compared the resulting risk levels.

The establishment of safety standards (maximum permissible contaminant levels) for chemicals in drinking water has generally, been based on the assumption that ingestion is the primary route for human exposure. However, recent research has shown that inhalation exposure, during water use activities like dish washing, showering and bathing, can have an equally significant, if not higher, impact on human exposure (Lee et al., 2009). Also, exposure due to dermal absorption of chemicals during dish and hand washing, showering, bathing have been shown to be comparable to direct ingestion of water. Villanueva et al. (2006) found that bladder cancer risk tended to be higher for exposure through showering, bathing and swimming in pools compared with drinking of water, but differences were small. Inhalation or dermal absorption may lead to a higher concentration directly in target organs (e.g., kidney, bladder, or colon), bypassing efficient detoxification steps in the liver that occur upon ingestion. The lowest contribution to the total cancer risk was due to dermal uptake (Tokmak et al., 2004). We estimated the risks for four exposure scenarios: minimum, lower bound, central tendency, upper bound and maximum. In this study, central tendency scenario, cumulative risk for dermal route was 2.11×10^{-9} ; for inhalation route it was 1.75×10^{-6}; and for ingestion route it was 8.91×10^{-8}. Inhalation exposure had the most significant impact on human exposure; then ingestion, and then dermal exposure. Traditional risk

assessments of water often consider only ingestion exposure to toxic chemicals, but scientists proposed that inhalation and dermal absorption be considered in the risk assessment of drinking water Uyak (2005). Tokmak et al. (2004) and Lee et al. (2004) found that oral ingestion is the pathway most hazardous to human health in terms of cancer risk of THMs. On the other hand, Lee et al. (2006) conducted a study about risk assessment for THMs species in drinking water in Taiwan. In the exposure assessment calculation, inhalation was found as the principal pathway. The next pathway was ingestion followed by dermal intake.

One of the important factors in for inhalation exposure is transfer efficiency of THMs from water to air. There are several studies to estimate of chloroform levels in the air by using a volatilization factor (Legay et al., 2011; Uyak, 2005; Tokmak et al., 2004). For instance, Legay et al. (2011) used the same volatilization factor for each THM compound to calculate the concentration of component in the air. Very few studies are available characterizing volatilization of chemicals during bathing / showering, and in washing machines and dishwashers. One of them is McKone's (1987) model. According to McKone's (1987) model transfer efficiency data for different compartments (shower, bathroom and the main house) has been calculated. Major factors that contribute to the volatilization of a contaminant were the water flow rate used, the temperature of the water, and the contaminant's volatility, expressed by its Henry's constant.

Another important exposure pathway associated with tap water is the absorption of contaminants through the skin during water use activities. Primary activities resulting in skin contact with contaminated water are bathing and showering which have contact area as the whole body surface; secondary activities are dish and hand washing which have contact area as hand surface area. In this study, the activities of showering, bathing and washing hands were considered for dermal exposure analysis. Chemical Specific Permeability Coefficient (K_ps) for the outermost layer of the skin was used as a measure of a contaminant's capacity to permeate through it. Lee et al. (2004) used a permeability of 0.0020m/h; but it was not chemical specific. Another study was conducted by Lévesque et al. (2000). As a result, overall water to skin permeability was reported to be 0.22 cm/h for each component. However, USEPA (1997) recommends chemical specific permeation. We used K_ps values recommended by the USEPA (2003) (see Table 5.12).

Risk assessment requires calculation of the chronic daily intake. Chronic daily intake (mg/kg/d) is the combination of water contaminant concentration (mg/L), average daily intake rate of drinking water (L/d) and the body weight (kg). In our study, we used measured values of these three input variables to estimate chronic daily exposure in each exposure scenario considered. However, there are some studies in the literature which used constant values for one or more of these variables. Lee el al. (2006) assumed an intake rate of 2,5 L/day. Tokmak et al. (2004), Uyak (2005) and Legay et al. (2011) also used constants for these variables. Therefore, the risk levels reported in these studies do not reflect the variation in the population in terms of these variables.

In general, there are three broad sources of uncertainty: scenario uncertainty, model uncertainty and variable uncertainty. Scenario uncertainty involves the inferences selected for the exposure scenarios. Model uncertainty refers to the uncertainty due to the mathematical model used to estimate the exposure-risk or a dose-response relationship. Variable uncertainty refers to uncertainty for the values of the variables in the exposure or risk model (USEPA, 1997). In our study uncertainties were not calculated. The uncertainties may be studied as a future study.

Probabilistic approach involves using probability distributions to represent each variable in exposure and risk equations. The range of values these are input variables and weight of these values by their probability of occurrence are concerned. In this study, instead of random sampling from input variable distributions to simulate the exposure-risk model probabilistically, we constructed five exposure scenarios: minimum, lower bound, central tendency, upper bound, and maximum. Minimum and maximum exposure scenarios considered the minimum and maximum values of each input variable that would minimize or maximize the model output (exposure-risk) value, while similarly 5^{th} and 95^{th} percentile values were used in lower and upper bound scenarios. The central tendency scenario used the median value of each input variable to calculate a 50^{th} percentile exposure-risk value. Therefore, exposure-risk values that may be considered as the estimations for İzmir population. As a future study, Monte-Carlo simulation may be employed to probabilistically estimate the population risks. This way, an uncertainty analysis can be conducted to estimate scenario and variable uncertainty.

Total carcinogenic risk for drinking-water has been calculated as a measure of the probability of incurring a disease caused by THMs. The two methods for cumulative

/ total risk assessment (the simple addition and CRPF) were compared. CRPF method is a new method that combines the principles of dose addition and response addition into one method to assess mixture risks for multiple route exposures. Dose addition method groups contaminants with a common mode of action into subclasses. The mode of action differs across the subclasses, but the toxicological end point (or outcome) is the same. For each subclass, an index chemical is selected to be representative of that subclass. In this study, dose addition was applied but response addition was not applied because THMs are thought to have a similar toxicity mechanism for carcinogenic effects. Dose addition is applied within each subclass. However, a toxicity normalized addition based on an index chemical approach was proposed instead of a simple addition. Here, the selection of the index chemical is an important step. The mixture component with the largest and most confident body of knowledge was proposed to be selected as the index chemical (Teuchler et al., 2004). Teuchler et al. (2004) used trihalomethanes as an exemplary application. They selected bromodichloromethane as the index chemical because it has the strength and complete toxicity data and the same mode of action as the other members of the subclass. Therefore, we also used it as the index chemical in this study. The total risk levels estimated by the simple addition method were an order of magnitude higher than those of by the CRPF method. This is a very large difference in terms of pollution/risk management, therefore a special attention should be paid to the method used to estimate cumulative or total carcinogenic risks for THMs.

Presence of THMs was reported in many studies, whereas only a few studies estimated exposures and risks such as Legay et al. (2011) in Canada, Lee et al. (2004) in Hong Kong, Tokmak et al. (2004) in Ankara, Uyak (2005) in İstanbul. In all these studies, the cumulative / total risks estimated using the simple addition method. Among THMs, chloroform is the most frequently detected, generally the largest-concentration compound which indicates the presence of other DBPs. Legay et al. (2011) found that chloroform was the major by-product in the air to which people are exposed during showering and bathing activities, since it has a lower boiling point than the other three THMs. Concentration of chloroform in drinking water varied between 14.1 μg/L and 155.9 μg/L in their study. There were two scenarios: cancer risk with chloroform and cancer risk without chloroform, because carcinogenity of chloroform at drinking water levels was considered as not appropriate by the USEPA (1997). Inclusion of chloroform seriously increases the carcinogenic risk for surface water source, chlorinated drinking

waters. In our study, we have not included chloroform as recommended by the USEPA (1997). At maximum exposure scenario, chloroform concentration of inhalation was 517µg/L in our study, which (similar to what Legay et al. [2011] reported) resulted in a very high chronic toxic risk levels (HQ=16.7) for inhalation. We have considered volatilization of all THMs, while Legay et al. (2011) considered only chloroform.

Lee et al. (2004) estimated chronic-toxic risks for ingestion and dermal absorption routes. The average total non-carcinogenic risk level (Hazard Index, HI=0.35) was below the threshold level of HI=1. In this study, HQ was calculated for chloroform for ingestion, inhalation, and dermal routes. The median HQ values were ranked from high to low as inhalation route ($HQ=7.99\times10^{-3}$), ingestion route ($HQ=1.92\times10^{-4}$) and dermal route ($HQ=9.45\times10^{-6}$ - 4.14×10^{-7}). The lifetime total cancer risks calculated for total THMs were 2.00×10^{-5} with simple addition method and 1.84×10^{-6} with CRPF method. Lee et al. (2004) reported an average carcinogenic risk value of 9.76×10^{-5} calculated by the simple addition method including chloroform. The risks observed by the additive method were generally in agreement with other literature values. Risk values greater than one in a million (10^{-6}) are generally considered unacceptable by the USEPA (2000b). USEPA (2000b) have the flexibility to adopt water quality criteria that result in a risk level higher than 10^{-6}, ensuring that highly exposed groups do not exceed a target 10^{-4} risk level. Four categories were identified for the unit cancer risk. $R_T < 10^{-6}$ No action is needed. $10^{-6}<R_T < 5.10^{-5}$ and $5.10^{-5}<R_T <10^{-4}$ represent generally acceptable levels of carcinogenic risk and the related zones are considered at low priority. $R_T > 10^{-4}$ The cancer risk level is unacceptable and action is required. The total carcinogenic risk values estimated in this study using CRPF method were 5.73×10^{-11}, 8.53×10^{-10}, 1.84×10^{-6}, 3.80×10^{-4}, and 6.77×10^{-4} for minimum, lower bound, central tendency, upper bound, and maximum exposure scenarios. The first two are below the action limits set by the USEPA, the latter three are above the action limit, whereas all were an order of magnitude lower than those estimated by the simple addition method.

CHAPTER 7

CONCLUSIONS

In İzmir drinking water, total carcinogenic risk has been calculated for four THM species (chloroform, BDCM, DBCM, and bromoform) and for all three exposure routes (ingestion, inhalation and dermal). Exposure pathways of drinking water ingestion, inhalation and dermal absorption during bathing, showering, dish and hand washing were included.

Traditional risk assessments for drinking water often considered only ingestion exposure to toxic chemicals. In this study, inhalation was found as the principal exposure route. The next route was ingestion followed by dermal absorption. In the inhalation exposure estimates, uncertainty was reduced because transfer efficiency was used for better estimation of volatilization. Similarly, permeability coefficient, variability of population characteristics (body weight, skin surface area, age), water behavior patterns (consumption water, ingestion rate) in the studied samples were integrated in the risk assessment, instead of using constants, to decrease the uncertainty.

The total risks for carcinogenic THMs were calculated by two methods which were simple addition method and CRPF method under five exposure scenarios. We concluded that the total carcinogenic risk calculated by additive method was an order of magnitude higher than the CRPF method. In Izmir, for minimum and lower bound scenarios, the results of the both methods were below the action limit which were between 9.28×10^{-9} - 5.73×10^{-11}. For central tendency scenario, both methods indicated that the risks may be considered as low priority. On the other hand upper bound and maximum exposure scenarios resulted in different values. Because the total carcinogenic risk calculated by the simple addition method was $>1\times10^{-3}$ it was unacceptable and requires action. The total carcinogenic risk calculated by CRPF method was ($>1\times10^{-4}$) an order of magnitude lower than the simple addition method but still in the unacceptable region requiring action. The estimated total risks indicate that the local water authority needs to better control the formation of disinfection by-

products in the treatment plant and at the boosting stations and/or consider process modification in the plant.

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