Chlorinated Water and Overall Risk of Cancer: A Systematic Review

Gordon David Parbery

BSc, Grad. Dip. Human Nutrition and Dietetics

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The Joanna Briggs Institute, Faculty of Health Sciences,

The University of Adelaide

Welcome to Country*

Welcome to Kaurna Country
Ninna Marni (A Kaurna word for "hello, how are you?")

I would like to Acknowledge that the land we meet on today is the traditional lands for the Kaurna people and that we respect their spiritual relationship with their Country. I also acknowledge the Kaurna people as the traditional custodians of the Adelaide region and that their cultural and heritage beliefs are still as important to the living Kaurna people today.

*Reconciliation South Australia. 2016. Welcome and acknowledgement of country. Available: http://www.reconciliationsa.org.au/learn/welcome-and-acknowledgement-of-country- [accessed 11 August 2016].

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Executive summary

Introduction

Chlorine was introduced into large-scale public water supplies early in the 20th century as an inexpensive and expedient solution to render sewage contaminated and infectious water supplies non-infectious. Redraw and recycling of contaminated and infectious water downstream continues to this day around the world e.g. Mississippi River, United States (US) and the Murray-Darling River, Australia. However, today disinfection of redrawn water with chlorine allows consumption of recycled water without causing gastrointestinal epidemics including cholera and typhoid. Trihalomethanes, sourced from chlorinated water drawn from the bottom of the Mississippi River in New Orleans, were first identified in 1974 as the potential carcinogenic agents responsible for the very high rates of cancer occurring there. Since then chlorine disinfection by-products (CDBs) have been a serious public health concern. Exposure to them is widespread and associated with increased cancer risk and adverse reproductive and developmental outcomes. To date increased cancer risk has only been confirmed for bladder and colorectal cancers. The objective of this review is to determine the evidence for an association between chlorinated water and cancer, other than colorectal and bladder.

Method

The Joanna Briggs Institute methodology for systematic reviews was used, with multiple databases date limited to 1974. Data was included according to an *a priori* protocol, and was synthesized through meta-analysis or presented narratively.

Results

Twelve statistically significant point estimates were identified: all reported cancers combined risk index 1.13 (1.07, 1.2) $p = 0.000$, geographical regions of North America and Europe, for males and females as well the following cancer sites breast, female

reproductive, melanoma, non-Hodgkin's and lung. Non-Hodgkin's and lung had significant predictive intervals.

Overall, for all reported cancers a relative increase in risk of 13% was observed. This risk is discussed in terms of the absolute incident and mortality associated with CDBs.

Conclusion

The results from the present work support the association between CDBs and cancer originally made by Rook in 1974 and strengthen the argument for a causal basis.

Recommendations for best practice

The US Environmental Protection Agency (US EPA) since 1974 has been proactive and set the benchmark for regulating CDBs to reduce population risk and exposure. Despite the encouraging action of the US EPA the overwhelming attitude towards disinfection of water supplies with chlorine in public health and within the water industry generally remains one of, "infection control is paramount and in no way should be compromised to lower exposure risk to CDBs". Large urban populations prospered without the need to disinfect water supplies with chlorine for centuries including throughout the 19th century. However, CDBs are now considered a serious public health concern and are recognised in the US as contributing to the burden of chronic non-communicable diseases; including cancer now at epidemic rates. The results of our systematic review help put scale and magnitude to the potential size of the problem. Improved knowledge of biologically safe water, new technology and the hygienic management of sewage to prevent contamination of water supplies will help mitigate the need for disinfection. Ongoing research to determine the most desirable water qualities for health and how to deliver this quality of water to end users will set the gold standard to strive for in the entire water supply chain.

Declaration

I, Gordon David Parbery certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Gordon David Parbery

March 2016

Acknowledgements

Ice crystals shimmered and tinkled. The old Chinese sage had risen, dusted his cloak and pushed back the hood covering his brow. He surveyed the bleak winter landscape. Little birds and animals, drawn by his warmth in the night scattered. Golden light arced into the sky and the sun peeked over the distant sparkling horizon. A new day had begun

Anon.

My journey into academia, beginning this time as it did at the age of 51 has been an interesting one to say the least. Those who know me will understand. I could hold Trish McReynolds responsible, her various, assorted and sundry colleagues and their shenanigans.

I owe much to the ancient ways and friends who have taught me along the path. Glynn Braddy and associates first and foremost, helped to reveal a unique perspective and world view even if old as the world itself. There are others I am extremely grateful to for their incredible support and insight also.

I met Grandpa Charlie Thom, Red Tailed Hawk Walking Backwards into the Future on arrival to California in 1991. Grandpa Charlie cooked me until I was more than done, in the sweat lodge. Then passed me to his son Bobby Lake-Thom (Medicine Grizzly Bear), who continued to teach me high up on the side of Mt. Shasta in Northern California. I was in my thirties and had never met an Aboriginal person from Australia. Bobby guided me back to the land down under and I met Uncle Moogy and Aunty Irene but not before I had travelled to London, Paris and Italy and tasted the waters of the Thames, Seine and in Rome, drank from the Fontana Di Trevi as well as the Tiber.

My father passed over in 1992 at the age of 60 and my mother continued living in Alabama, US. She turned eighty in April 2016 and I was with her to celebrate. There I met her good friend Tom Hendrix, and learnt from him about the Singing River and the Yucchi, first people of Alabama.

I travelled the entire length of the Murray Darling River system with Uncle Moogy. My daughter danced with Aboriginal people all up and down the river. I reported my experiences for continuing education credits as part of my professional learning and development as a clinical dietitian and shortly after was expelled though the adverse finding is contested.

My wife and her towering support drive me. We have been through thick and thin and celebrate 27 years of marriage this year. Our daughter teaches me every day how to be a better dad.

This work could not have been achieved without the enduring patience of my supervisors David Tivey and Alexa McArthur, for that I am grateful. However, there are others including supervisors' integral to the success of the project. Ed Aromatis and Tim Schulz, my original supervisors and without whose input, the nature of the investigation as it became, might never have occurred. The original question posed remains, "Is chlorinated water hydrating?" A clue now, to what the answer may be is clearly exposed. Between the desired urgency of Ed and the measured pace of Dave the thesis evolved. Whenever I need copy editing Alexa McArthur is always ready to insert comma's no matter where I wanted or needed!

Mick Draper, Maria Albanese and all of the library staff also supported the work immensely as did many of the Joanna Briggs Institute administrative staff.

Thank you to all for making it happen.

Gordon David Parbery

2016

There is no truth.

Anon., Joanna Briggs Institute
May 2013 research school

Truth is a contentious issue. Nothing is absolutely proven, and the progress of proof is based on repeated revisions, corrections and the rejection of beliefs that were once regarded as 'the truth'.

Glynn Braddy

Chapter 1: Introduction

Suar cuar' for the 'Colara'

To cuar the Colara put your feet in hot water and drink as much hot tee or hot water as you can and lap yourself between blankets. Suar Cuar.

Evan's Journal 1852-1892

(McCarthy 2015)

Importance of water

Water is positioned second only to oxygen in terms of priority and importance to our very existence. Without food one might survive weeks, however without water survival is reduced dramatically to days and without air to a matter of minutes. If food is defined to include both water and air, then the nutritional hierarchy of vital nutrients immediate to life becomes starkly clear.

Origins of chlorinated water

Chlorine was introduced into large-scale public water supplies early in the twentieth century as a cheap and expedient solution to render contaminated and infectious water supplies non-infectious (Water Quality and Health Council 2016). This in turn eliminated the need to invest capital into the development of infrastructure necessary to hygienically manage sewage and source water supplies (Hansen 2016a; Lemon 2016).

Redraw and recycling of contaminated and infectious water downstream continues to this day, for example in the Mississippi River, United States (US) and the Murray-Darling River, Australia. However, today disinfection of redrawn water with chlorine allows consumption of the recycled water without causing gastrointestinal epidemics including

cholera and typhoid.

Microbial origins of disease and introduction of disinfection: Semmelweis and others

Medical practice in 19th century London was based on Victorian era social principles which had evolved from the Georgian era and was dominated by the gentlemen physicians of the Royal College (established in 1518) who practiced with little or no regard for hygiene or sanitation, accepted then as the norm (Marsh 2015; White 2016). These conditions prevailed throughout European cities at the time. Contrasting the norm is the story of Semmelweis (1818-1865), a Hungarian physician working in Vienna, Austria and known as the "saviour of mothers", who was one of the first to convincingly demonstrate the merits of chlorine disinfection. While employed at the First Obstetrical Clinic of the Vienna General Hospital, Semmelweis meticulously researched the association between hygiene and maternal deaths. His interpretation of the data he collected led to the formulation of the practical application of hygienic principles including disinfection with chlorine in midwifery and hospital obstetrics practice. This laid the foundation for infection control that is now taught to modern medical students around the world for this reason (Benedek 1983; Best and Neuhauser 2004). Although well documented Semmelweis' success was not without detractors. Indeed, the medical elite refused to accept his methods and ultimately dismissed him. Sadly, he was beaten to death, for promoting the success of his research and after being admitted into an insane asylum. How many lives were lost because of ignorance and an unwillingness to consider the merit of his work? It was years after his death before his work was fully accepted and became standard practice (Best and Neuhauser 2004; Science Museum 2016). It was not until the 1950's that the importance of Semmelweiss's work was officially recognised with the renaming of the hospital in Budapest (Hungary), to become the Semmelweiss University of

Medicine at the Medical Faculties bicentennial. Further university mergers occurred in 2000 and the resulting institution renamed Semmelweiss University (Semmelweis University 2016). Other greats in defining the link between microbiological causes of infectious disease in the Victorian era were Robert Koch (1843-1910, German), Louis Pasteur (1822-1895, French) and Max von Pettenkofer (1818-1901, German). A great rivalry amongst these and many others over microbiology and the causes of infectious disease, laid the foundation for modern medicine, disinfection and hygienic practice.

Impact of urbanisation

Industrialisation led to rapidly growing cities and an overwhelming burden of sewage that exceeded the capacity of the rudimentary if any, infrastructure for managing sewage. Industrialisation also changed the biological nature of sewage (Lemon 2016). As populations migrated from agrarian based communities into the large urban centres of Europe in the 18th and 19th centuries diets began to change which in turn changed faecal biology and the organic nature of sewage (Wilson 2011). Waterways prior to industrialisation had natural capacity to manage biological organic loads without becoming contaminated or infectious; however, as regional population centres evolved into urban centres and cities such as London, the sewage burden grew and evolved accordingly (City of Westminster Archives 2016). By the end of the 18th century, the horse populations associated with large cities (e.g. 50,000 and 100,000 for London and New York, respectively) had also grown, contributing to the overall sewage burden. Again this impact changed the biology and composition of sewage possibly contributing a pro and pre-biotic effect to the biology of waterways this sewage entered and to those exposed to this water (Johnson 2016; National Institute of Health 2016). The influence of source water exposure on the human microbiota remains to be fully understood. However, urbanisation

significantly changed the profile of organic material entering waterways. The advent of chlorine disinfection created a new chemical exposure burden to humans and their microbiome in the form of chlorine disinfection by-products (CDBs) generated as a result of chlorination (National Institute of Health 2016; Richardson and Postigo 2012; Richardson et al. 2007).

It was in this setting that the relationship between water, sanitation, hygiene and health began to evolve. Especially the need to address dysenteric disease such as cholera and typhoid (Table 1 and 2). In London, it was common for water inlets, used to draw water for public supply from the Thames River, to be placed close to and downstream from sewage discharge outlets. This resulted in the return of faecal contaminated water back into the supply for consumption. With a concentrating effect the further down river the water was extracted.

The use of chlorine to disinfect is remarkably effective. However, chlorine disinfection masks the underlying problem, unsanitary conditions which stems from lack of knowledge and practice of basic principles of hygiene.

Early management of water supply systems

The overwhelming sewage contamination of waterways, cholera epidemics and belief in the miasma theory of contagion, led the English parliament in 1846 and inspired by Edwin Chadwick to pass the Nuisances Removal and Diseases Prevention Act, known as the Cholera Bill (Lemon 2016). Chadwick, regarded at the time as a pioneering public health campaigner was appointed to the London Metropolitan Sewers Commission. He subsequently ordered all cesspools and sewage pits in London cleared and dumped into the

Thames River. This exacerbated sewage contamination and pollution of the river and London's water supply and is now credited as the critical turning point that caused the great stink of 1858 (Hansen 2016a, b).

Link between water and cholera

John Snow, (1813-1858) in 1854 removed the handle from the Broad Street water pump in London and is credited with ending the cholera epidemic occurring in that area as a result. However, it was many years later before his hypothesis that cholera was transmitted via contaminated water and not by air or "miasma" was accepted. Similar to Semmelweiss, Snow was outside of the medical elite, this resulted in a reluctance to consider his hypothesis as a viable explanation of the cause and effect (Bingham et al. 2004). Later it was discovered the well for the Broad Street pump was too shallow and positioned next to an old and leaking cesspit that had previously been exposed to cholera contaminated faeces (Bingham et al. 2004).

Cholera is eradicated from London without chlorine!

Good luck, good fortune, good planning, or coincidental? London prospered for centuries including throughout the 19th century on water sourced primarily from the Thames River without disinfecting it with chlorine (City of Westminster Archives 2016; The Gazette Official Public Record 2016). Despite this there were only four recorded cholera epidemics in London during the 19th century (City of Westminster Archives 2016). The British parliament in 1858 was forced by the catastrophic conditions of the Thames River and the great stink to act urgently. The solution was to develop a system to hygienically manage London's sewage (Lemon 2016). The result was major public works to construct the embankment, which began in 1859 and took 20 years to complete. The embankment is

regarded as the largest public works of the 19th century anywhere in the world (Hansen 2016b). An unintended impact of improved sewage management was elimination of the cholera epidemics from London. Although the last recorded cholera epidemic in London occurred in the East End in 1866, this was an area of London that had yet to be connected to the newly constructed sewer works (Hansen 2016b). Sewage from the River Lea was identified as the source of sewage contamination and cause of this epidemic. The reservoirs of the East London Water Company which supplied the East End sourced water from the Lea River (Daniel and Markoff 2016).

As a result, the resolution of cholera epidemics was an inadvertent by-product resulting from the improvement in public hygiene and sanitation and the separation of sewage from source water (Hansen 2016b). Cholera had been eradicated without disinfecting water with chlorine and the large scale introduction of chlorine disinfection of public water supplies did not begin until many years later at the beginning of the 20th century.

Large scale chlorination of public water supplies begins in the 20th century

Large scale chlorination of public water supplies was first introduced in the US in Jersey City, New Jersey in 1908 (Water Quality and Health Council 2016). However, it did not happen without a legal dispute over responsibility for bearing the cost of eliminating sewage contamination of the source water (Water Quality and Health Council 2016). The dispute was over the cost of infrastructure development to resolve the contaminated source water supply and who would pay for it; the water company (Jersey City Water Supply Company) or the city. The water supply company won the court decision on the basis chlorination would cost “a mere $5.60 per day for Jersey City’s 40 million gallons daily usage” page 7 (Water Quality and Health Council 2016) and therefore avoided the expense

of building sewer works to prevent sewage from contaminating the source water reservoir (Boonton Reservoir, New Jersey). Chlorination of sewage contaminated source water rendered the water non-infectious and rates of dysenteric infections especially typhoid and cholera decreased. This set the precedence for the current practice of chlorine disinfection of public water supplies, which became commonplace in the US and Europe in the early 20th century (American Chemistry Council 2012a).

Chlorine disinfection masks the underlying problem of sewage contaminated source water by rendering infectious water non-infectious. However, the same result can be achieved with adequate infrastructure for managing sewage hygienically and ensuring separation from water supplies (City of Westminster Archives 2016; Lemon 2016).

Chlorine: A great public health triumph or not?

Although chlorine disinfection of sewage contaminated or infectious public water supplies is regarded as one the great public health triumphs of the 20th century, evidence has been accumulating that may now contradict this opinion (Tomasz 2009; USEPA 2015; Water Quality and Health Council 2016). Chlorination is inexpensive requiring moderate infrastructure to achieve large scale dosing of public water supplies. This contributed to its rapid introduction across the America's and Europe (Water Quality and Health Council 2016). Its use is reinforced by today's knowledge that sanitary and hygienic practice are critical to preventing infectious disease. Application of this knowledge underpins water management including infrastructure development from catchment, throughout the supply and distribution chain including effluent discharge into the environment.

If there is adequate infrastructure, that can ensure a clean water supply, is there still a need

for routine use of chlorine to disinfect water? Disinfection is an insurance against exposure to infectious agents from ingestion and use of potable water. Potable water may be safe to drink without the need for disinfection. Disinfection is essential only if potable water is contaminated with sewage or is infectious. The routine addition of chlorine is now a public health concern because of the known adverse health consequences. Chlorine is a highly reactive chemical species and combines with organics in the water. The result is a complex chemical milieu of chlorinated organics (CDBs). The composition and potential toxicity of the mix is driven by the source of environmental organic compounds including those of anthropogenic origin (Richardson and Postigo 2012; Richardson et al. 2007). Chronic and widespread exposure to CDBs may have supplanted the health concerns regarding infectious agents. Indeed, researchers are raising concerns about the potential adverse health consequences particularly cancer and pregnancy complications (Richardson and Postigo 2012; Richardson et al. 2007; Tomasz 2009; USEPA 2015).

One hundred years later and the (re) discovery of chlorine disinfection by-products in 1974

The fundamental science of microbial disinfection of water supplies with chlorine remains unchanged. The advances have been restricted to refining the chlorine dosing regimens and water processing technology (American Water Works Association 2011). These changes have been driven by a need to satisfy consumer demand for safe, high quality, palatable and acceptable water. However, any reduction in chlorination regimen has been tempered by concern for disease outbreaks associated with potentially infectious water supplies (NHMRC 2011; USEPA 2015; WHO 2011).

Today ninety-eight percent of potable water in the US relies on chlorine-based disinfection technologies derived from the Victorian era (circa. 19th century) and the situation in most

developed water supplies around the world is the same (American Chemistry Council 2012b; Villanueva et al. 2015). Concerns about the human (and environmental) health consequences of chlorine-disinfected water including awareness of CDBs were originally raised when large-scale chlorination of public water supplies first began but were dismissed because of the overriding success at reducing dysenteric outbreaks (American Chemistry Council 2012a; Race 1918). It was not until 1974, when Rook identified the high incidence of cancers in New Orleans (the highest in the US at the time), and associated this with high levels of a class of CDBs (Trihalomethanes (THMs)) in the water supply (Rook 1974). New Orleans residents were exposed to high levels of CDBs due to the cities location at the bottom of the Mississippi River. This is a result of water recycling throughout the length of the river. Rook adjusted the exposure for potential confounders (e.g. industrial pollution) and concluded there was a statistically significant association between cancer and exposure to CDBs (Rook 1974).

Rook's findings caused great controversy at the time (DeRoun T. A. 1975; Marx 1974; USEPA 1974, 1975, 2004). However, the national research and surveillance of water treatment and distribution across the US and around the world proceeded immediately, and with urgency. A deeper understanding of the chemistry associated with chlorination, including the formation of CDBs and the adverse health consequences associated with them has evolved from this time. Despite the controversy over the original findings a direct result of Rook's work was the introduction of the Safe Drinking Water Act (US) at the end of 1974 (Table 3) (American Water Works Association 2011; USEPA 1974, 2004, 2015).

Chlorine disinfection by-products: What are they and how toxic can they be?

Chlorine disinfection by-products result from chemical reaction of chlorine with various

constituents of water including naturally occurring organic matter, bromine, iodine and anthropogenic compounds (Richardson et al. 2007). Approximately 600 CDBs have been identified, most remain to be chemically characterised (Richardson and Postigo 2012). Some are extremely toxic such as N-nitroso dimethylamine (NDMA) a nitrosamine (Agency for Toxic Substances & Disease Registry 1989; McDonald and Komulainen 2005). A gap in knowledge of CDB mixtures and their toxicity is an area of concern requiring research (Richardson and Postigo 2012; Richardson et al. 2007). In the US eleven CDBs are regulated, based on their association with adverse health outcomes. These regulated chemicals include the THMs, typically the most abundant fraction of CDB formed accounting for approximately 14% of the total CDB load. At 12% the second most abundant form is the haloacetic acids (HAAs) (Figure 1). Chapter 3 outlines in detail the cancer risk associated with known CDBs determined by both the US EPA and International Agency for Research on Cancer (IARC) (IARC 2004; USEPA 2015, 2016a, b).

Quest for knowledge accelerates

Since the discovery of THMs in 1974 and their association with chlorinated water and cancer, the public debate and quest for knowledge has accelerated to resolve the potential health concerns associated with CDBs. In the US, a series of intensive conferences held between 1975 and 1987 orchestrated by Jolley, the US EPA and others, helped set the scene for investigation (Jolley 1975, 1977, 1979, 1983, 1984, 1987). To date an increased risk for cancer that is associated with CDB exposure has only been confirmed for bowel and bladder cancers (Hrudey et al. 2015; Morris 1992; Rahman et al. 2010; USEPA 2005a, 2006b, 2015; Villanueva et al. 2003). The evidence-base has continued to grow however, as documented in 18 reviews (Amy et al. 2000; Bull et al. 1995; Cantor 1997; Clark et al.

1986; Crump and Guess 1982; Grellier et al. 2015; Hrudey and Fawell 2015; Koivusalo and Vartiainen 1997; McMichael 1990; Melnick et al. 1994; Mills et al. 1998; Nieuwenhuijsen et al. 2009; Villanueva et al. 2015; Villanueva et al. 2001; Villanueva et al. 2004; Wigle 1998; Wilkins et al. 1979; Williamson 1981), several meta-analyses (Morris 1992; Rahman et al. 2010; Villanueva et al. 2003), and reviews published by the International Agency for Research on Cancer and World Health Organization (IARC 2004; World Health Organization 2007).

Many questions remain unresolved regarding possible impact on health with exposure to chlorinated water and the associated CDBs, mostly due to methodological drawbacks of the conducted research. Grellier et al. (Grellier et al. 2015) have outlined in detail potential errors in study design, reporting methods and exposure analysis, all of which continues to obscure the strength of the association between chlorine-disinfected water and increased cancer risk. In addition to Grellier, reviews by Villanueva (Villanueva et al. 2015) and Hrudey (Hrudey et al. 2015; Hrudey and Fawell 2015) have attempted to put the current state of knowledge in perspective. However, CDBs in the environment remain an important public health issue to this day (Richardson and Postigo 2012; USEPA 2015; Villanueva et al. 2015; Villanueva et al. 2014). This has been compounded by acknowledgement that inhalation and dermal exposure routes (swimming, bathing and showering) should be considered as of equal, or of greater significance to ingestion (Villanueva et al. 2007).

Ominous predictions

CDBs are now considered a serious public health concern and are recognised in the US as contributing to the burden of chronic non-communicable diseases (NCD), including,

cancer as well as reproductive and developmental health risks (USEPA 2006b). Several amendments to the Safe Drinking Water Act of 1974 have been made since it was first introduced (Table 3), and the stage two disinfection by-products rule came into effect in 2006 to further reduce health risks associated with CDBs (USEPA 2006b).

The US EPA estimates these amendments will reduce the number of fatal and non-fatal cases of bladder cancer preventing approximately 280 cases per year, of which 26% are predicted to be fatal. Based on bladder cancer alone, stage two disinfection by-products rule is estimated to provide annualized monetized benefit of US$763 million to US$1.5 billion (USEPA 2006b). Extrapolation of the calculation used to estimate these figures to other cancers, as well as reproductive and developmental adverse outcomes, begins to put the scale and magnitude of the problem in perspective.

The increasing body of evidence linking serious public health consequences to disinfecting water with chlorine including increased risks of cancers and reproductive concerns are ominous (Tomasz 2009; USEPA 2015). The adverse health complications may be as great if not greater than the dysenteric epidemics chlorine disinfection supposedly resolved. Chlorine disinfection was only required if the source water was infectious primarily as result of being contaminated with sewage (Lemon 2016; Water Quality and Health Council 2016).

Epidemics: Dysenteric or cancer?

Cancer incident and mortality rates around the globe are at epidemic proportions and the global burden of cancer is predicted to double by 2030 (American Cancer Society 2016; IARC 2014; Servan-Schrieber 2016). Dysenteric epidemics of the past including cholera

and typhoid were shown to be eliminated long before the introduction of large scale chlorine disinfection of water supplies began at the beginning of the 20th century. This was achieved when hygienic principles of sanitation were applied to source water supplies specifically to prevent contamination by sewage (Hansen 2016b). Cholera epidemics in London ceased in 1854 when John Snow removed the Broad Street water pump handle (Daniel and Markoff 2016). Although the last cholera epidemic in London occurred in 1866 the cause of this was clearly identified as sewage contamination in the East End water supply and because the East End had not been connected to the newly constructed sewer system (Hansen 2016a, b).

Exposure to water disinfected with chlorine is now widespread (Villanueva et al. 2015). The scale and magnitude of possible adverse health outcomes remains to be understood fully.

Overview, the aim and objectives

The objective of this study was to systematically review all selected databases and literature sources using the Joanna Briggs Institute methodology for quantitative systematic reviews. This methodology draws on peer reviewed articles, grey literature and any other relevant sources to find relevant studies and data associated with exposure to chlorine-disinfected water and cancer. Risks associated with colorectal or bladder cancers and CDBs have already been established and therefore were not considered in this systematic review (Hrudey et al. 2015; Morris 1992; Rahman et al. 2010; USEPA 2005a, 2006b; Villanueva et al. 2003).

The US EPA acted immediately and with urgency in 1974, based on the limited evidence

of the relationship between water disinfected with chlorine and cancer. Since then, evidence has continued to build to include bowel and bladder cancers and adverse pregnancy complications and the US EPA has continued to lead the world to reduce exposure and therefore risk of adverse health outcomes associated with CDBs (USEPA 2015). As such, the objective of this review, is to determine the strength of the association between exposure to chlorine-disinfected water and cancers, other than bladder or colorectal.

Relevance to the profession: Biologically safe water and health?

Emphasis in healthcare around the world is shifting as the burden of infectious disease is being overtaken and replaced by the increasing burden of chronic NCDs previously associated with developed and now more so with developing economies around the world (Pruss-Ustun A 2008). In 2012, 68% of all deaths globally (39 million) were attributed to NCDs, an increase of 8% since 2000. Cancer is included in the top four causes of death by NCDs (WHO 2016).

Water and its management traverses the realms of infectious and NCDs as a public health concern. Current methods relying on chlorine to disinfect infectious water supplies, may be deferring the underlying public health challenge of hygienically managing sewage. Humans have prospered for centuries including in highly dense populations when water supplies remain uncontaminated with sewage, non-infectious and biologically safe (City of Westminster Archives 2016; Lemon 2016). Safe, biologically active, rather than biologically inactive water (resulting from disinfection with chlorine) may prove to be the most nourishing form of water for human kind (Lemon 2016; Stanwell-Smith 1997).

The contribution of CDBs exposure to the global burden of disease both infectious and NCD is important to understand to resolve as the scale and magnitude of the problem, which is currently not clearly defined or understood. The current global cancer epidemic and widespread exposure to CDBs is evidence and suggests the scale of the problem could be large (American Cancer Society 2016; Servan-Schrieber 2016). When reproductive and developmental health risks are factored, the gravity of the problem and overall risk to public health becomes clear.

Given the nutritional hierarchy of water, second only to oxygen, and its importance to overall health a safe and health promoting water supply is paramount. Anything that compromises this should raise a red flag for policy makers to review and redefine priorities in terms of research and public health policy (Malcolm et al. 1999). There is a need to act urgently as significant efforts and capital expenditure are currently underway in many countries to meet the millennium development goals of the United Nations target 10; water and sanitation. This target continues to rely on chlorine disinfection technology developed over a century ago. Continuing to incorporate this technology into infrastructure developments could perpetuate the burden of disease and transfer it from infectious to non-communicable as a result (Beaglehole et al. 2011a; Beaglehole et al. 2011b; Pruss-Ustun A 2008). New insights into the microbiology of humans, the human microbiota, and its importance to health may reveal fundamental relationships previously not considered between humans, microbiology and water (National Institute of Health 2016).

Uncertainty or certainty? What is the evidence?

Since 1974, from the research and policy changes that followed on from Rooks research and discovery, it is becoming increasingly clearer there is merit to the public health concerns over the adverse health consequences associated with chlorine disinfection of

water (USEPA 2015). The scale and magnitude of these is yet to be fully comprehended; however, early indications are they could be considerable (USEPA 2015). Ongoing research will continue to reveal the total contribution to the global burden of disease.

Level of evidence differentiates the Systematic Review

This thesis represents a systematic review of the literature focused on elucidating the association of exposure to chlorinated water and cancer. It is differentiated from prior works by considering all cancer sites, excluding bowel and bladder. With the aim of performing a meta-analysis, this work also attempts to estimate the level of risk associated with exposure to chlorinated water and identify knowledge gaps for future work. Results are discussed in the context of best practice and implication for human health.

Ranking of research according to quality has evolved from the work of David Sackett (1934 – 2015) regarded as one of the founding "fathers" of modern clinical epidemiology and evidenced-based medicine (McMaster University 2016) along with Archie Cochrane (1909 – 1988) (Shah HM 2009) and Alvan Feinstein (1925 – 2001) (Yale Bulletin & Calendar 2001).

The Joanna Briggs Institute ranks quality of evidence based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group (GRADE Working group 2004) and from this has created the Joanna Briggs Institute levels of evidence and grades of recommendations classification system (The Joanna Briggs Institute 2014).

As such, systematic reviews applying the Joanna Briggs Institute methodology provide the structural basis and format for synthesising heterogenic sources of evidence from a range of study designs including observational studies from epidemiology as is the case with this

review. The primary research selected for critical appraisal and meta-analysis consists entirely of cohort and case control study designs, constituting the “likely best available evidence” (The Joanna Briggs Institute 2014).

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Tables

Table 1: Deaths from Cholera in London (Bingham et al. 2004)

Table 1 Deaths from cholera in London, registered from 23 September 1848 to 25 August 1849.

Sectors of London	Population in 1841	Deaths from cholera	Death rate per 1000 inhabitants
West	300,711	533	1.77
North	375,971	415	1.10
Central	373,605	920	2.46
East	392,444	1597	4.07
South	502,548	4001	7.96
Total	1,945,279	7466	3.84

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Table 2: Effect of Chlorination on Typhoid rates per 100,000 population (Race 1918)

City	Before	Period	Commenced Chlorination	Period	After	Percentage reduction
Baltimore	35	1900-10	June 1911	1912-15	22	36
Cleveland	35	1900-10	Sept 1911	1912-16	8	77
Des Moines	23	1900-10	Dec 1910	1911-13	13	41
Erie	51	1900-10	Mar 1911	1912-14	15	70
Evanston, Ill.	29	1908-11	Dec 1911	1912-13	15	50
Jersey City	19	1900-17	Sept 1908	1909-16	8	55
Kansas City, Mo	43	1900-10	Jan 1911	1911-16	14	66
Omaha, Neb	23	1900-09	May 1910	1911-16	11	53
Trenton	46	1907-11	Dec 1911	1911-16	29	35
Montreal	40	1900-10	Feb 1910	1911-16	25	37
Toronto	31	1900-10	Apr 1911	1912-16	8	75
Ottawa	50	1900-10	Sept 1912	1913-17	17	50
Mean	34				15	45

Table 3: Chronology of Amendments to the Safe Drinking Water Act 1974: Changing USA Regulations Chlorine Disinfection By-Products Total Trihalomethanes (TTHM) and Haloacetic Acids (HAA5) Maximum Contaminant Level (MCL)

Chlorine CDBs First associated with adverse health effects by Race in 1918(Race 1918) then linked to cancer in 1974 by Rook et al (Marx 1974; Rook 1974) and more recently with reproductive concerns(USEPA 2006b)	Pre 1974 Refer to US Public Health Service(USPHS) most recent guidelines published1962. 1969 USPHS surveyed 1000 public water systems serving approximately 12% of the population and found 41% did not meet the 1962 guidelines.	1974 SDWA (Safe Drinking Water Act) introduced establishes National Primary Drinking Water Regulations (NPDWR) legally enforceable standards for public water supplies with 15 or more connections or that regularly serve 25 or more residents.	1979 Total Trihalomethane Rule	1998 Stage 1 Disinfection By-Products rule	2002 Long Term 1 Enhanced Surface Water Treatment Rule	2004	2006 Long Term 2 Enhanced Surface Water Treatment Rule Stage 2 CDBs rule	2016 All systems to be compliant with long term 2 and stage 2 rules within 12 months of 2016
TTHM (MCL) (Chloroform, Bromoform, Bromodichloromethane, Chlorodibromochloromethane)			100 µg/l (100 ppb) Applied to water systems serving 10,000 or more people, smaller systems were not regulated at this time	MCL reduced to 80 µg/l (80 ppb) and applied to all community water systems and phased in over time	Large water systems have to meet MCL	All others have to meet MCL	No change to MCL but changes to monitoring and infrastructure to meet or exceed the requirements	
HAA5 (MCL) (Monobromoacetic acid MBAA, Monochloroacetic acid MCAA, Dichloroacetic acid DCAA, Trichloroacetic acid TCAA, Dibromoacetic acid DBAA)			n/a	MCL 60 µg/l (60 ppb)				

American Water Works Association A. 2011. Water quality & treatment : A handbook on drinking water. 6th ed. New York ; Sydney:McGraw-Hill.
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Chapter 2: Systematic review protocol

Systematic Review Protocol

The protocol served two purposes. It outlined the plan and scope of the systematic review subject to peer review process of the JBI Library. This was used to inform an expert panel to determine the appropriateness of the research topic for Master's candidature at the University of Adelaide. I defended the protocol in 2012. In attendance were supervisors, post graduate coordinator for JBI and two experts external to JBI, one in the field of epidemiology and the other, water treatment.

References in this chapter are in the Vancouver style as required by the JBI library.

Protocol was accepted for publication in 2012

Citation for protocol

*Parbery G, Tivey D, McArthur A. 2012. Epidemiological association between chlorinated water and overall risk of cancer: A systematic review. The JBI database of Systematic Reviews and Implementation Reports 10:259-272.

Statement of Authorship (Appendix 5)

JBI Library of Systematic Reviews

Review title

Epidemiological association between chlorinated water and overall risk of cancer: A systematic review.

Reviewers

Gordon Parbery [1]

Dr David Tivey[2]

Alexa McArthur[2]

[1]Gordon Parbery, BSc, Post Graduate Diploma Human Nutrition and Dietetics, MSc Clinical Science Candidate, The Joanna Briggs Institute, Faculty of Health Sciences, The University of Adelaide, South Australia. Australia 5005. Contact: gordon.parbery@adelaide.edu.au

[2]The Joanna Briggs Institute, Faculty of Health Sciences, The University of Adelaide, SA5005. Contact: davidtivey@adelaide.edu.au or alexa.mcarthur@adelaide.edu.au

Review objective

The review objective is to synthesise the best available evidence on exposure to chlorinated water and risk of cancer. Risks associated with colorectal or bladder cancers have already been established and therefore will not be considered in this systematic review.

Background

Public large scale use of chlorine-disinfected water began in the early years of the 20th century and resulted in dramatic reductions in observed rates of dysentery causing diseases, particularly cholera and typhoid infections[1]. Today in the USA 98% of water treatment plants use chlorine-based disinfectants to treat water[2] and similar chlorine disinfection use patterns of water treatment occur around the world where developed systems of potable water exist. The clear reduction in dysentery causing diseases derived from chlorine disinfection of water supplies offset complaints about chlorination adversely influencing the taste of water, environmental impacts and concerns regarding potential adverse health effects[1,3-8].

Race in 1918 was the first to suggest that chlorine disinfection by-products could be the basis for these complaints[1]. The science of chlorine disinfection by-products was in its infancy at this time, as was the chlorine disinfection process. It was not until Rook in 1974[9] identified trihalomethanes as the potential carcinogenic agents in potable waters sourced from the Mississippi River in Louisiana (New Orleans) that chlorine disinfection by-products came under scrutiny as an important public health risk[4,10-12].

The potential public health risks of large scale chlorination treatment of water supplies were first alluded to by Race in 1918[1] but was poorly understood due to the limited knowledge base of the time. Although the knowledge base has grown, many questions remain unresolved regarding the toxicity, carcinogenicity and incidence of cancer associated with exposure to trihalomethanes and other chlorine disinfection by-products. As a result, they remain an important public health issue to this day[1,3,4,6-8,10,13].

Water is fundamental to life, the extensive use of chlorine disinfection practices globally results in widespread exposure to chlorine treated water and therefore chlorine generated disinfection by-products. Early studies focused on ingestion as the exposure route however,

dermal (showering, bathing, dishwashing and swimming) and inhalation (vaporized aerosols as created in showering, dishwashing, indoor swimming pools, spas and saunas) are now also regarded as important exposure routes[13-17]. As a result, early trial reports and study designs may have underestimated exposure to chlorine by-products and the impact these may have on cancer incidence and mortality. Indeed, inhalation exposure at swimming pools has been linked to a threefold increase of cancer risk (all cancers) above the USA EPA negligible risk level[18]. Villanueva's research on trihalomethanes, highlighted that dermal exposure was associated with a 2x increased risk for bladder cancer in men who showered or bathed with chlorinated water whether or not they drank chlorinated or bottled water[13,16-18]. The route of exposure also influences blood concentration and target tissue levels of chlorine disinfection by products[14]. The knowledge base continues to expand as these exposure routes are given more consideration in study design.

Irrespective of exposure route, the evidence for an association between chlorine by-products and bowel/bladder cancers is increasing[13,19,20]. It is estimated one in three cancers globally are skin cancers[21] the leading cause of cancer in Australia and the world. Skin cancers have been excluded from the following cancer statistics because of the generally accepted view that skin cancers are associated with depleting ozone layers and exposure to ionising radiation[21]. However, the association to dermal and inhalation exposure to chlorination disinfection by-products as a possible cause of skin cancer has not been previously considered as a risk factor since these routes of exposure have only recently been identified[21].

In Australia bowel cancer is the most common cancer after skin cancer affecting approximately 13,000 men and women each year[22]. According to the International Agency for Research on Cancer's Globocan 2008 project, colorectal cancer is the third most common cancer in men and second most common in women worldwide[23]. Almost 60% of cases occur in developed regions, the highest rates being estimated in Australia / New Zealand and Western Europe[23]. Stomach cancer ranks as the fourth most common diagnosed worldwide and second for cause of death worldwide[23]. In 2008, the most common cancers (excluding skin cancers) in descending order were lung, breast, colorectal and stomach. Oesophageal cancer ranked eighth for diagnosed and sixth for cause of death worldwide[23]. Chlorine disinfection by-products are also being investigated for possible association with other cancers including bladder, kidney, liver, pancreatic, leukemia, breast, gastrointestinal and lymphoma[6,19,24-45]. The fact that dermal and inhalation routes of exposure can have significant influence on cancer risk and have only recently begun to be considered raises the question of the role chlorine disinfection by-products have as a risk factor if any in the development of skin cancer?

Chlorine disinfection by-products result from chemical reaction of chlorine with various constituents of water including naturally occurring organic matter, bromine, iodine and anthropogenic compounds[13]. Eleven disinfection by-products are currently regulated in the USA based on the potential association with adverse health outcomes. These include the trihalomethanes, the most common chlorine disinfection by-products formed and several haloacetic acids[13,46]. Two of the trihalomethanes, bromodichloromethane and chloroform, have been classed as 2B carcinogens (possibly carcinogenic to humans) by the International Agency for Research on Cancer (World Health Organization)[6] whereas the US Environmental Protection Agency has designated bromodichloromethane and bromoform as B2 carcinogens

(probably carcinogenic to humans as evaluated using the U.S. EPA's 1986 Guidelines for Carcinogen Risk Assessment)[18]. The haloacetic acids, dichloroacetic acid and bromate have been graded by both agencies as 2B (possibly carcinogenic to humans) and B2 (probably carcinogenic to humans as evaluated using the U.S. EPA's 1986 Guidelines for Carcinogen Risk Assessment) respectively[6,18]. The International Agency for Research on Cancer has graded two trihalomethanes, bromoform and chlorodibromomethane as 3 (not classifiable as to its carcinogenicity in humans)[6].

In addition, over 600 disinfection by-products have been identified and it is estimated that many more than this exist and remain to be identified[13]. The toxicological data therefore is incomplete. The knowledge base for the USA regulated disinfection by-products is also inadequate, for example; Bromoacetic acid has never been tested for carcinogenicity and the remaining regulated disinfection by-products have not been graded either by the International Agency for Research on Cancer or the US Environmental Protection Agency[6,13,18,46]. Seventy- four disinfection by-products are defined as "emerging" by Richardson due to their moderate occurrence levels and/or toxicological properties[13]. One of the most toxic chlorine disinfection by-products identified to date are the halofuranones and analogues, known as MX and BMX series[13,47] as assessed in animal studies designed to monitor formation of a variety of cancers and in vitro cell assays[13]. Of those disinfection by-products that have been identified, concentrations range from sub micro grams per litre to micrograms per litre[13].

Current knowledge of the carcinogenicity, genotoxicity and mutagenicity of chlorine disinfection by-products is a result of studies[13] with standardised microbial and mammalian cell lines and cytology tests. As such, the mode of action of these compounds within the body therefore is poorly understood. The potency of individual or mixtures of disinfection by-products, how these damage DNA and consequently interfere with cellular function leading either to carcinogenesis, mutagenesis or genotoxicity in a range of sites remains the subject of study. Gender, age, dose and duration of exposure appear to have the most influence based on current knowledge as to what potential negative health outcome is likely to be experienced. There is very little research on how complex mixtures of disinfection by-products interact and potentially compound their toxicity. This is now recognised as an area requiring further research since it is a realistic reflection of what occurs in practice[13].

The US EPA and other groups have applied risk assessment models to disinfection by-products and potential adverse health outcomes[18]. In general, the following four steps of analysis have been applied, hazard identification, dose response assessment, exposure assessment and risk characterization[13]. In the USA results from risk assessment models have been used to make changes to the regulated disinfection by-products in drinking water out of concerns for cancer and reproductive and developmental risks associated with exposure [8,13,15,48,49]. The US Environmental Protection Agency introduced these revisions to the national primary drinking water regulations in 2006[8,46].

In Australia there is no mandatory regulation of drinking water standards. The Australian Drinking Water Guidelines 2011[3] was recently updated to include more information on potential toxic chemicals in tap water; The guide has been designed as the authoritative reference for good practice and management of drinking water supplies in this country[3]. Consumers today are better informed and have increasing awareness of the potential contribution disinfection by- products and other contaminants (including new and emerging

contaminants such as endocrine disruptors, pharmaceutical and personal care products, mixtures of organic chemicals, perfluorinated chemicals and nanoparticles) may play in adverse health outcomes including carcinogenesis and reproductive complications[3,4,8,13, 43 49]. The current version of the Australian Drinking Water Guidelines 2011 devotes 750 pages (of 1244 pages) to discussing potential toxic chemicals in tap water including disinfection by products[3]. Evidence of consumer knowledge exists by the common use of water filters at home and office and the extensive use of bottled waters all of which either remove chlorine and other contaminants or do not contain chlorine. The point of use treatment of water or use of alternatives like bottled water is a global phenomenon in developed nations.

Today there is evidence implicating chlorine disinfection by-products in a range of adverse health outcomes including many cancers, genotoxicity and abnormalities associated with pregnancy including birth defects15,49. Asthma, eye, skin and mucus membrane irritations, allergic reactions, endocrine effects, infections and respiratory complications have also been implicated50-52. However, the magnitude of these effects is not clear and there are many gaps in the knowledge base requiring more research13. The strongest associations with cancer to date have been made with colorectal and bladder cancers16,19,20 and appears to be related to dose and length of exposure based on relative risk6. Routes of exposure, especially dermal and inhalation are now considered by some as potentially of more consequence than that of ingestion13-17. The possibility that skin cancer is related to exposure does not seem to have been considered to date since most early studies focused on ingestion only as route of exposure. Only recently have studies begun to look at new and emerging chlorine disinfection by-products and although these may occur in much smaller concentrations than the trihalomethanes and other more common disinfection by-products they can be as much as 6000 times more toxic as is the case with the halofuranone MX when compared with chloroform according to the cancer potency index developed by the state of California 13,47.

It is the intent of this review to systematically assess the current knowledge base for research that has addressed the relationship between chlorine disinfection by-products exposure and possible association with cancers, other than colorectal and bladder, and determine the strength of evidence for an association.

Inclusion criteria

Types of participants

This review will consider studies that include males and females of all ages.

Types of intervention(s)/phenomena of interest

This review will consider studies that evaluate exposure to chlorine disinfection by-products by drinking (ingesting), bathing, showering, swimming, cooking, cleaning and dishwashing (dermal and inhalation) and identify incidence and mortality outcomes of cancer (excluding colorectal and bladder) compared with exposure without chemical disinfection (chlorine) or alternative disinfection processes.

Types of outcomes

This review will consider studies that include the following outcome measures.

Incidence, mortality and specifically measures of risk between exposure and outcome of cancers with the exception of bowel and bladder. For example, the following cancers have

been associated with chlorine disinfection by-products, kidney/adrenal, liver, thyroid, pituitary, lymphoma and leukemia, pancreatic, gastrointestinal (other than colorectal), testicular, breast and lung cancer. These and any other cancers identified as relevant e.g. skin cancers will be included.

Types of studies

This review will consider epidemiological prospective and retrospective cohort studies and case control studies for inclusion.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilised in this review. An initial limited search of PubMed will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe articles. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review. Studies published since trihalomethanes were first identified as drinking water disinfection by-products in 1974 will be considered for inclusion in this review. Any other studies found and considered relevant will also be included.

The databases to be searched include the following but are not limited to them:

PEER REVIEWED

SCOPUS

Cochrane Library

Web of Science

Embase

PubMed

GOVERNMENT DATA BASES

USEPA Office of Ground Water and Drinking Water (water.epa.gov/drink/index.htm)

US Department of Health and Human Services

US Department of Agriculture (USDA) Rural Development Utilities Programs, Water and Environmental Programs (www.usda.gov/rus/water)

Health Canada; www.hc-sc.gc.ca/ewh-semt/water-eau/drink-potab/index-eng.php

European Union; http://ec.europa.eu/environment/water/-drink/index_en.html

Australia; www.nhmrc.gov.au/publications/synopses/eh19syn.html

WATER INDUSTRY

American Water Works Association (AWWA); www.awwa.org

Association of State Drinking Water Administrators (ASDWA); www.asdwa.org

Association of Metropolitan Water Agencies (AWMA); www.amwa.net

National rural Water Association (NRWA); www.nrwa.org

National Association of Water Companies (NAWC); www.nawc.com

Water Research Foundation; www.waterresearchfoundation.org

GREY LITERATURE

Mednar grey

World Health Organization; www.who.int/water_sanitation_health/dwqn/en

Proquest dissertations & Theses database

Trove

Conference Proceedings

EXAMPLES OF KEYWORDS:

Disinfection by-products, disinfection by product*[tw], chlorinat*[tw], chlorine[tw], chlorine/chemistry[mh], purification by product*[tw], water supply[mh], water suppl*[tw], water purification*[tw], drinking water[tw],potable[tw], treated water*[tw], exposure, dermal, inhalation, ingestion, swim*[tw], bath*[tw], shower*[tw], human*[tw], trihalomethanes, haloacetic acids, bromate, chlorite, halonitromethanes, Iodo-acids, halo acids, Iodo- trihalomethanes, halofuranones, halomides, haloacetonitriles, tribromopyrole, nitrosodimethylamine, nitrosamines, aldehydes, chlorate etc

Neoplasms, kidney, liver, lung, breast, skin etc.

Search modifiers “and” “or” etc. will be applied.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data collection

Data will be extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix II). The standardised data extraction tool will be modified as necessary if it does not suit the study requirements for data extraction. The data extracted will include specific details about the exposure, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible be pooled in statistical meta-analysis using Revman 5.1 (The Cochrane collaboration). All results will be subject to double data entry. Measures of association including odds ratios, rate ratios, standardised incidence ratios, hazard ratio, risk ratios, will be considered relative risk. If required, extracted data will be transformed into Ln (Relative risk) with standard errors calculated from available data using the method described by Greenland[53]. If effect estimates are not available, they will be calculated from crude data and the 95% confidence limits. Where possible, effect measure adjusted for maximum

number of covariates will be extracted. Heterogeneity will be assessed statistically using the standard Chi^2 and I^2 and also explored using subgroup analyses based on the different study designs, primary cancer site diagnoses and whether or not secondary metastases have been accounted for in mortality records. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Conflicts of interest

No conflicts of interest are known.

Acknowledgements

TGB & Associates for an introduction to the element of water. Ed Aromatis and Tim Schultz for help refining the question, although the original question remains, is chlorine disinfected water hydrating? Hao-min Cheng for taking on the critical role of secondary reviewer.

As this systematic review forms partial submission for the award of Masters of Clinical Science through the Joanna Briggs Institute, the University of Adelaide, a secondary reviewer will only be used for critical appraisal.

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Appendix I: Appraisal instruments

MAStARI Appraisal instrument

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

		Yes	No	Unclear	Not Applicable
1.	Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2.	Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3.	Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4.	Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5.	Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6.	Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7.	Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
9.	Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix II: Data extraction instruments

MAStARI data extraction Instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal_____ Record Number_____

Study Method

RCT	☐	Quasi-RCT	☐	Longitudinal	☐
Retrospective	☐	Observational	☐	Other	☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Chapter 3: Chlorinated water and overall risk of cancer: A systematic review

Chlorinated water and overall risk of cancer: A systematic review

The following chapter is the manuscript in its entirety submitted for publication to the open source journal Environmental Health Perspectives (EHP) on 24 March 2016. The submission is in process. A final determination of acceptance is yet to be made.

As such the formatting of the document adheres to the author rules for submitting to this journal including referencing style (EHP publication) and font (times new roman, 12).

In addition to the material submitted to EPH, appendices for the thesis include all excluded articles (Appendices 1-3). All remaining non-significant forest plots have also been included for completeness (Appendix 4).

Statement of Authorship (Appendix 5)

Chlorinated water and overall risk of cancer: A systematic review.

Gordon David Parbery, Alexa McArthur, David Tivey

The Joanna Briggs Institute, Faculty of Health Sciences, The University of Adelaide, SA. Australia 5005.

Contact: gordon.parbery@adelaide.edu.au

Corresponding Author

Gordon Parbery

Mail Address: 43 Bandon Tce, Marino, SA. 5049

Telephone: 61+ 408896023

Email: gordon.parbery@adelaide.edu.au

Short Running Title:

Chlorinated water and overall risk of cancer.

Abstract

Background

Trihalomethanes derived from chlorinated water were first identified in 1974 as potential carcinogenic agents in the United States. Exposure to disinfection by-products created by disinfecting water with chlorine is widespread and an important public health concern.

Objective

To determine the evidence for an association between chlorinated water and cancer, other than colorectal and bladder.

Method

The Joanna Briggs Institute methodology for systematic reviews was used, with multiple databases date limited to 1974. Data was included according to an *a priori* protocol, and was synthesized through meta-analysis or presented narratively.

Results

The systematic search located 751 articles, and 33 studies met the criteria for review. Meta-analysis results for 24 combined studies returned twelve statistically significant point estimates including the following: all cancers combined risk index 1.13 (1.07, 1.2) p = 0.000, geographical regions of North America and Europe, for males and females as well the following cancer sites breast, female reproductive, melanoma, non-Hodgkin's and lung. Non-Hodgkin's and lung had significant predictive intervals.

Overall, for all reported cancers a relative increase in risk of 13% was observed. This risk is discussed in terms of the absolute incident and mortality associated with chlorine disinfection by-products.

Conclusions

These results reflect the most reported cancers globally, and provide evidence in support of the association between chlorine disinfection by-products and cancer, strengthening the possibility this relationship could be causal. However, lack of granularity in the reporting of cancer diagnoses and exposure data introduces significant heterogeneity in the meta-analyses and prevent making this a definitive conclusion.

Introduction

Public large-scale use of chlorine-disinfected water began in the early years of the 20th century and resulted in dramatic reductions in observed rates of dysentery causing diseases, particularly cholera and typhoid infections (Race 1918). Today in the United States (US), 98% of water treatment plants use chlorine-based disinfectants to treat water (American Chemistry Council 2012) and similar chlorine disinfection patterns of water treatment occur around the world where developed systems of potable water exist (Villanueva et al. 2015). As a result, there is widespread exposure to chlorinated water and the disinfection by-products created by disinfecting water with chlorine.

Concerns regarding the public health risks associated with exposure to chlorinated water, were first raised by Race in 1918 (Race 1918). Trihalomethanes (THMs) were first identified in 1974 as potential carcinogenic agents in potable waters sourced from the

Mississippi River in Louisiana, US (New Orleans), and chlorine disinfection by-products (CDB) came under scrutiny as an important public health risk (Rook 1974). The highest rates of cancer in the US were focused in New Orleans, Louisiana at this time (DeRoun T. A. 1975; Marx 1974; USEPA 1974, 1975, 2004). Based on these reports, the Environmental Protection Agency (EPA) acted swiftly and imposed regulations to reduce CDBs in drinking water in the US immediately (USEPA 1974, 1975, 2004). A series of intensive conferences held between 1975 and 1987 orchestrated by Jolley, the US EPA and others, helped set the scene for intensive investigation (Jolley 1975, 1977, 1979, 1983, 1984, 1987). As a result, the US leads the world in regulating CDB levels in potable water. This has been based on the results of Rook and ongoing findings correlating CDB with cancer, pregnancy complications and other potential adverse health outcomes (Rook 1974; Tomasz 2009; USEPA 2005a, 2015). The World Health Organization (WHO) has published guidelines regarding CDBs, and countries around the world are following the US lead (WHO 2011).

To date an increased risk for cancer that is associated with CDB exposure has only been confirmed for bowel and bladder cancers (Hrudey et al. 2015; Morris 1992; Rahman et al. 2010; USEPA 2005a, 2006b; Villanueva et al. 2003). The evidence base has continued to grow, as documented in 18 reviews (Amy et al. 2000; Bull et al. 1995; Cantor 1997; Clark et al. 1986; Crump and Guess 1982; Grellier et al. 2015; Hrudey et al. 2015; Koivusalo and Vartiainen 1997; McMichael 1990; Melnick et al. 1994; Mills et al. 1998; Nieuwenhuijsen et al. 2009; Villanueva et al. 2015; Villanueva et al. 2001; Villanueva et al. 2004; Wigle 1998; Wilkins et al. 1979; Williamson 1981), several meta-analyses (Morris 1992; Rahman et al. 2010; Villanueva et al. 2003), and reviews published by the International Agency for Research on Cancer and World Health Organization (IARC 2004; World Health

Organization 2007). Many questions remain unresolved regarding possible impact on health with exposure to chlorinated water and the associated CDBs, mostly due to methodological drawbacks of the conducted research. As a result, they remain an important public health issue to this day (Richardson and Postigo 2012; USEPA 2015; Villanueva et al. 2015; Villanueva et al. 2014).

Early studies focused on ingestion as the exposure route; however, inhalation of volatile CDBs and dermal (showering, bathing, dishwashing and swimming) exposure are now regarded as important exposure routes (Leavens et al. 2007; Villanueva et al. 2007). As a result, early trial reports and study designs may have underestimated exposure to CDBs and the impact these might have on cancer incidence and mortality. Indeed, inhalation exposure at swimming pools has been linked to a threefold increase of cancer risk (all cancers) above the US EPA negligible risk level (USEPA 2005). Villanueva's research on THMs highlighted that dermal exposure was associated with a doubling of the risk for bladder cancer in men who showered or bathed with chlorinated water whether or not they drank chlorinated or bottled water (Villanueva et al. 2007). These routes of exposure have been demonstrated to increase blood concentration and target tissue levels of CDBs (Leavens et al. 2007).

Cancer is a leading cause of mortality around the world and the global burden of cancer is expected to nearly double by 2030. In 2014 the International Agency for Research on Cancer estimated global age standardized incidence and mortality rates of 182 and 102 per 100,000 population respectively (IARC 2014). Excluding non-melanoma skin cancer, among men the five most common sites of cancer diagnosed in 2012 were the lung (17%), prostate (15%), colorectal (10%), stomach (9%), and liver (8%). In contrast among

women, the five most common incident sites of cancer were breast (25%), colorectal (9%), lung (9%), cervix (8%) and stomach (5%). For all cancers combined the highest incidence rates are associated with the high-income countries of North America and Western Europe together with Japan, the Republic of Korea, Australia and New Zealand. The four major cancers that affect populations in North America are the same as those in Europe: prostate, breast, lung and colorectal (IARC 2014).

The World Cancer Research Fund International claim approximately a third of the most common cancers can be prevented through lifestyle choices including; diet, maintaining a healthy weight and taking regular physical activity (World Cancer Research Fund 2015).

Chlorine disinfection by-products result from chemical reaction of chlorine with various constituents of water including naturally occurring organic matter, bromine, iodine and anthropogenic compounds (Richardson et al. 2007). Approximately 600 CDB have been identified. Eleven are currently regulated in the US based on the association with adverse health outcomes. These include the trihalomethanes, typically the most abundant fraction of CDB formed accounting for approximately 14% of the total CDB and several specific haloacetic acids, which constitute the second largest known fraction making up approximately 12% (Figure 1). Two of the trihalomethanes, bromodichloromethane and chloroform, have been classed as possibly carcinogenic to humans (2B carcinogens) by IARC (WHO 1991) whereas, the US EPA has designated bromodichloromethane and bromoform as probably carcinogenic to humans (B2 carcinogens) (USEPA 2005, 2016b). The haloacetic acids, dichloroacetic acid and bromate have been similarly graded by both agencies as 2B (possibly carcinogenic to humans) and B2 (probably carcinogenic to humans) respectively. IARC has designated the THMs bromoform and

chlorodibromomethane to be not classifiable as to their carcinogenicity in humans (IARC 2004; USEPA 2015). Although both IARC and the US EPA have attempted to describe the risk associated with exposure to chlorinated water with their respective classification systems, they are based on insufficient evidence and do not include any toxicology for the 86% of CDB, which are not trihalomethanes. Many are now known to be greater than 1,000 times more toxic than any of the THMs; for example, the halofuranones and analogues, known as MX and BMX series are regarded to be 6,000 times more toxic than chloroform according to the cancer potency index developed by the state of California and some nitrosamines (N-nitroso dimethylamine, NDMA) and haloquinones more toxic than the halofuranones. (Agency for Toxic Substances & Disease Registry 1989; McDonald and Komulainen 2005; Richardson and Postigo 2012; Richardson et al. 2007; Wang et al. 2013).

Given the number of CDBs (Richardson et al. 2007) and the potential combinations of these, the toxicological data therefore is incomplete. The knowledge base for the US regulated disinfection by-products is also incomplete; for example, Bromoacetic acid has never been tested for carcinogenicity and the remaining regulated CDBs have not been graded either by the IARC or the US EPA. Seventy-four disinfection by-products are defined as “emerging” by Richardson due to their moderate occurrence levels and/or toxicological properties (Richardson et al. 2007).

The mode of action of CDB compounds within the body is poorly understood. The potency of individual or mixtures of CDB, how they damage DNA, interfere with cellular function potentially leading to carcinogenesis, mutagenesis or genotoxicity is still to be defined (Richardson et al. 2007). Although interesting, the mechanism of action will have little

impact regarding public health interventions to reduce cancer risk. A greater concern is verifying potential link s between CDB exposure and risk of cancer.

In summary there is evidence implicating CDBs in a range of adverse health outcomes including cancer (Florentin et al. 2011; Morris et al. 1992; Rahman et al. 2010; Richardson et al. 2007; Tomasz 2009; USEPA 2005a, 2015; Villanueva et al. 2003). To date, the strongest associations between CDB exposure and cancer have been made with colorectal and bladder cancers, and this appears to be related to dose and length of exposure. However, the evidence for other cancers is still to be synthesized; as such the magnitude of CDB effects associated with cancer incidence and mortality is unclear.

The intent of this review was to systematically assess the knowledge base for research addressing the relationship between CDBs and strength of association with cancers in humans, other than colorectal and bladder.

Method

This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) standards (Moher et al. 2009), (Figure 2). A three-step search strategy using the Joanna Briggs Institute methodology for systematic reviews was applied consisting of an initial limited search of PubMed, followed by analysis of text words contained in the title and abstract, and of the index terms used to describe articles (Supplemental Material Appendix 1). A second search using all identified keywords and index terms across peer reviewed and grey literature databases including PubMed, Embase, Scopus, Cochrane Library, Web of Science, ProQuest Dissertations and Theses Database, Mednar, World Health Organization, Trove, and Conference Proceedings. In addition,

selected Government and industry websites were searched for reports (Supplemental materials, Appendix 1). Finally, the reference list of all identified reports and articles were searched. Only studies published in English were included. The search strategy set out to find both published and unpublished studies since 1974 when trihalomethanes were first identified as drinking water disinfection by-products and associated with increased cancer incidence and mortality (Rook 1974) and was completed by March 2013. Automated search updates were established and at the time of writing no new studies meeting search criteria were identified

Inclusion criteria required reporting of cancer in humans as incident or mortality outcomes across all ages and genders based on exposure to chlorinated water.

Assessment of methodological quality

Selected papers for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute (The Joanna Briggs Institute 2014). The critical appraisal tool, meta-analysis of statistics assessment and review instrument (MAStARI) designed specifically for comparable cohort and case control studies minimizes bias and provides a quantitative assessment of study quality for inclusion. (Supplemental Material Appendix 2). This tool relies on nine questions to score such elements as the population in question, confounders and appropriateness of statistical measures applied. Papers scoring five or more yes answers were accepted, scores of six to seven yes answers were considered medium quality studies and papers scoring eight to nine yes answers were regarded as high quality. Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

Data extraction

Extracted data was entered into bespoke Microsoft Excel® spreadsheets and included study details, geographical location, water source, data collection period, exposure period, exposure indices for chlorinated water (Table 1), chemical species of chlorine disinfection by-product if available and concentrations of these as reported, populations, gender, any noted confounders, type of cancer reported and whether incident or mortality. With the exception of the article by Kukkula and Lofroth (Kukkula and Lofroth 1997) all extracted results were adjusted for confounders. These included the respective confidence intervals, standard errors or *p* values and included odds ratios, relative risk, correlation coefficients, regression analysis, mortality rates, incident rates and rate ratios. Data entry was crosschecked by a second reviewer.

Data synthesis

Data derived from populations with confirmed exposure to CDBs were compared with those who had no exposure to chlorinated water. Table 2 lists extracted CDB exposure indices for the population with confirmed exposure. Where studies reported risk measures for a range of CDB exposures, only those associated with a CDB exposure greater than the lowest reported confirmed exposure value were pooled. Data were meta-analysed (MA) using Comprehensive Meta-Analysis software version 2 (BioStat Inc 2006) based on Dersimonian and Laird's analyses (DerSimonian and Laird 1986). The unit of analysis was set to the included study therefore effect measure for any given study was pooled before performing across study meta-analyses. Based on the heterogeneity in study design a random effects model was selected *a priori*. The included studies had varying measures of relative risk including odds ratio, rate ratios, and risk ratios. The outcomes of the included studies were deemed to be rare and the distinction between measures of risk ignored

(Greenland S 1987). Data were combined following Ln transformation of the point estimate and standard error (Greenland S 1987). When necessary standard errors were estimated from the reported confidence limits (Higgins JPT 2011) or *p* values (Greenland S 1987). The term risk index (RI) has been used to describe the output of meta-analysis and composite nature of input effect measures. Heterogeneity was assessed for with Cochran's Q statistic, I^2 and Tau^2. For all included MA, predictive intervals were calculated according to methods described by Higgins (Higgins JPT 2011). Publication bias was addressed by including both grey and peer reviewed literature and performing Egger's regression for meta-analyzes that included more than ten studies (Higgins JPT 2011), as well as assessment of funnel plots (data not included). Sensitivity analysis was performed using a one study removed protocol. Papers not included for meta-analysis are presented in narrative form.

Results

Study Characteristics

The systematic search located 751 articles, and 33 studies met the criteria for inclusion (Figure 2). Table 2 presents the characteristics of the studies selected. Thirteen papers were excluded after assessment of methodological quality four because there was no eligible data to extract or because of errors identified in reporting, four had inadequate exposure indices detail, three duplicated research, one reported bowel and bladder cancer and one was not relevant. All cancer categories were reported, including all leading cancers in both sexes (lung, breast, colon, prostate, skin, liver, stomach and uterine) as well as specific cancers. The number of different cancers reported in any given study ranged from a single cancer to as many as twenty-six. Twenty-five papers reported statistically significant associations between CDB exposure and one or more of the reported cancer types whereas

seven found no significant association. One paper described their results as equivocal, either unrelated or weakly related (Marcus et al. 1998). Studies were either cohort (n =16), or case control (n=17). The overall methodological quality of included papers was high. Two (6%) scored five yes answers (of nine) and met inclusion criteria, nine (27%) scored six to seven yes answers and twenty-two (67%) scored eight to nine yes answers (Supplemental Material Appendix 2).

Papers were segregated by the way data was reported resulting in seven subgroups; odds ratio, relative risk, correlation coefficients, regression analysis, mortality rates, rate ratio and incident rates. Twenty-four papers reporting results as varying measure of relative risk for rare events were pooled for meta-analysis as described in methods. (Alavanja et al. 1977; Brenniman et al. 1979; Cantor et al. 1999; Chiu et al. 2010; Do et al. 2005; Doyle et al. 1997; Fagliano 1998; Goittlieb et al. 1982; Gottlieb and Carr 1982; Ijsselmuiden et al. 1992; Koivusalo et al. 1994; Koivusalo et al. 1995; Koivusalo et al. 1997; Koivusalo et al. 1998; Kukkula and Lofroth 1997; Liao et al. 2012; Marcus et al. 1998; Nelemans et al. 1994; Tao et al. 1999; Tsai et al. 2013; Vinceti 2004; Wilkins III and Comstock 1981; Yang et al. 1998; Young 1983), (Figure 2 and Table 2).

Nine papers were excluded from meta-analysis. Five because results were not reported as ratios (Bean et al. 1982; Cantor et al. 1978; Flaten 1992; Foster et al. 1997; Kool et al. 1981) and three because the regression models used were heterogenic (Carlo and Mettlin 1980; Clark et al. 1986; Wigle et al. 1986). Although the study by Infante-Rivard et al. (Infante-Rivard et al. 2001) reported odd ratios these were close to unity and confidence limits spanned unity when comparing average exposure levels less than 95^{th} percentile with $\geq 95^{th}$ percentile of THM level. It also was excluded for these reasons.

Populations - Geographical Regions

For studies included in meta-analyses countries were combined into three geographical regions, North America (US and Canada), Europe (Finland, Netherlands and Italy) and Asia (Taiwan and China). Nine countries in total are represented by the thirty-three included studies; US, Canada, Finland, Netherlands, Norway, Taiwan, China, England and Italy. Five of these included large representative national populations, (US, Canada, Finland, Netherlands and Norway); the remainder included distinct regions or sub-populations within country. Two studies looked at children only (Fagliano 1998; Infante-Rivard et al. 2001), neither made significant associations. Tao et al. reported on males only and reported statistically significant associations (Tao et al. 1999). Three reported on females only (Doyle et al. 1997; Marcus et al. 1998; Young 1983), two of these found significant associations and the third, by Marcus reported equivocal results. The remaining twenty-seven included both genders. Of these twenty considered all ages and seven specified age cohorts.

The combined population of 24 studies included in meta-analyses is approximately 80 million not including three Taiwanese studies (Taiwan total study population unable to be determined) and represents seven countries (US, Canada, Finland, Netherlands, China, Northern Italy, Taiwan) Table 3.

North America

The largest national study including approximately 180 million people was in the US (Cantor et al. 1978). The second largest national study, also from the US (Clark et al. 1986), included approximately 36 million people. Three reported from Iowa (Bean et al.

1982; Cantor et al. 1999; Doyle et al. 1997) covering the majority of the state's population. The articles by Bean et al. and Cantor et al. included approximately 1.9 million people. The Bean et al. article defined the population by race with over 98% being Caucasian, 1.2% African American and 0.3% other races. While the Cantor et al. article represents 67% of the 1980 population. Doyle et al. reports on 42,000 post-menopausal women aged 55 – 69 years. The other US studies covered populations located in the states of New York (1.8M (Alavanja et al. 1977), 1.0M (Carlo and Mettlin 1980)), Maryland (90K (Ijsselmuiden et al. 1992), 100K (Wilkins III and Comstock 1981)), Louisiana (1.2M (Goittlieb et al. 1982), 1.5M (Gottlieb and Carr 1982)), Illinois (1.1M Caucasians only (Brenniman et al. 1979)), New Jersey (7.5M from the 2983 census (Fagliano 1998)), North Carolina (1.4M representing 44% of females age 35 – 84 years (Marcus et al. 1998)) and Wisconsin (all female [n=16 058] deaths between 1972-77 (Young 1983)).

Three Canadian studies (Do et al. 2005; Infante-Rivard et al. 2001; Wigle et al. 1986), included populations representing six provinces (of ten) including Quebec and 69 cities (Canadian population 1995 approximately 29 million). Two of the three studies made no statistical association.

Every paper from the US (n=15) with the exception of two, Fagliano (1998) who made no significant association and Marcus et. al. (1998) whose findings were equivocal, reported statistically significant associations between CDB and a range of cancers (Table 2).

Europe

Finland contributed five studies (Koivusalo et al. 1994; Koivusalo et al. 1995; Koivusalo et al. 1997; Koivusalo et al. 1998; Kukkula and Lofroth 1997) covering the entire Finnish

population and subgroups of this (approximately 5 million people in the 1985 census), four of which reported statistically significant associations between CDB exposure and a range of reported cancers. The Netherlands contributed two studies (Kool et al. 1981; Nelemans et al. 1994) totalling approximately 5 million and 1.3 million people respectively. Both reported statistically significant findings. One study from England, (Foster et al. 1997) from the South West Peninsula counties of Devon and Cornwall, reported statistically significant associations. One study from Italy (Vinceti 2004) included 420,000 people from Northern Italy, and reported statistically significant associations. A study from Norway (Flaten 1992) reported on 97 of 454 municipalities including approximately 3 million people and also reported statistically significant associations.

Asia

Taiwan reported four studies (Chiu et al. 2010; Liao et al. 2012; Tsai et al. 2013; Yang et al. 1998) covering approximately 65 of 361 municipalities, three of which made no association. One study from China (Tao et al. 1999) based in Shanghai (12 million people in 1987) reported statistically significant associations.

Exposure Indices – Chlorinated Water

Eighteen different measures were used within the 33 included studies to determine exposure to chlorinated water including the type of CDB, exposure level and duration of the exposure as well as specific types of water (Table 1). Seven studies included chlorinated against non-chlorinated waters, and surrogate markers for chlorination were reported as surface water versus ground water in eight studies. Ground water usually contains little or no organic matter, a precursor to CDB's formation and therefore little or no CDBs. Ground water was typically reported as being non-chlorinated. Two studies

compared chlorinated ground water with non-chlorinated ground water (Brenniman et al. 1979; Gottlieb and Carr 1982). One study reported polluted versus non-polluted water, and in this included chlorinated or non-chlorinated water (Nelemans et al. 1994). Alternatively, chlorine either pre or post-treatment plant 3 studies, (Gottlieb and Carr 1982; Wigle et al. 1986; Young 1983) or CDB were used as the index of exposure. Measures of chlorination including total trihalomethanes (TTHM), the most prevalent CDB (Figure 1) or specific species of these (chloroform, dibromochloromethane, bromodichlormethane, bromoform) were reported as actual values obtained in the field or as extrapolated estimates derived by formulae based on historical records and sampling data (15 studies). Values used for TTHM concentrations ranged between 0-246 µg/l (ppb) and chloroform <3-287 µg/l (ppb). Chloroform is the most abundant species of TTHM (Figure 1).

Five studies reported exposure according to mutagenicity of the water, four from Finland (Koivusalo et al. 1994; Koivusalo et al. 1995; Koivusalo et al. 1997; Koivusalo et al. 1998), the fifth from China (Tao et al. 1999) also included chlorinated and non-chlorinated exposure indices.

One study reported on data from STORET (STOrage and RETrevial) (Clark et al. 1986; USEPA 2016a) in the form of carbon alcohol extract (CAE) and carbon chloroform extract (CCE). No other CDBs (e.g. haloacetic acids) or exposure indices were used as an indicator of exposure to chlorinated water.

Confounders

Thirty-two of 33 papers reported confounders (Supplemental Material Appendix 3), Kukkula and Lofroth (Kukkula and Lofroth 1997) the exception. The maximum number of confounders reported by any one paper was 15 (Flaten 1992). The average number of confounders across all 33 studies was seven and typically risk measures accounted for

degree of urbanicity, career and/or industrial exposure risk including mothers at home, income, education, smoking, alcohol intake and a range of dietary patterns. Recent studies (Chiu et al. 2010; Liao et al. 2012; Tsai et al. 2013) used an urbanization index (increasing density of urbanization is associated with cancer mortality (Greenberg 1983; Tzeng and Wu 1986)) to consolidate up to nine explanatory variables including population density, age, composition, mobility, economic activity and family income, educational level, environmental factors and health service related facilities into one index factor which is then then subdivided further into four levels of metropolitan, city, town or rural.

Meta-analysis

Meta-analysis results for 24 combined studies (all reported cancers, all geographical regions, males and females) reported as RIs 95% confidence limit (CL) are presented in Table 3 and Figure 3. These combined data for exposure to CDB and risk of cancer resulted in a statistically significant point estimate RI 1.125 (1.065, 1.190) $p = 0.000$. No individual study in this cohort contributed more than 6.5% to the overall point estimate; however, there is marked heterogeneity $I^2 = 95\%$ and $Tau^2 = 0.012$. Fifteen of the included studies returned statistically significant point estimates ($p < 0.05$), 13 of which demonstrated increased risk associated with CDB exposure while two indicated reduced risk. The remaining nine had point estimates close to unity and CL spanning unity (Figure 3). Impact of study design was assessed for cohort and case control designs for all cancers. The point estimates for both study designs was statistically significant. For the cohort design the point estimate (RI 1.146 (1.064, 1.230) $p = 0.000$) was five percentage points greater than that observed for case controlled studies (RI 1.100 (1.027, 1.178) $p = 0.007$). Heterogeneity scores for both study designs was significant (Table 3).

Due to the degree of heterogeneity and spread of individual point estimates within the combined 24 studies sub-group analyses were undertaken.

Sub-group Analyses

Point estimates and heterogeneity statistics from sub-group analysis are summarized in Table 3 and divided according to study design, geographical regions, gender and 27 cancer types although six of these were derived from single studies and therefore did not meet criteria for meta-analysis. Eleven additional statistically significant point estimates were derived from the sub-group analyses. With the exception of Asia: all cancers, which have been included for completeness only significant results are described in detail.

Impact of geographical region all reported cancers.

The MA for North American studies includes 11 US and one Canadian study (Figure 4). The point estimate for reported cancers was statistically significant RI 1.090 (1.024, 1.161) $p = 0.007$. Five of the 12 studies reported a statistically significant ($p < 0.05$) increased risk of cancer associated with CDB and contributed 32% to the point estimate. All five statistically significant studies were from the US. Three reported multiple cancer sites ranging from 11 to 18 (Doyle et al. 1997; Goittlieb et al. 1982; Gottlieb and Carr 1982) whereas the remaining two focused on single cancers, in the brain (Cantor et al. 1999) and pancreas (Ijsselmuiden et al. 1992).

The other six US studies made no association. In contrast, the Canadian study by Do (Do et al. 2005) which assessed only a single cancer; pancreatic reported a statistically significant risk reduction for it. This result contributed 13% to the overall risk index. Heterogeneity for the North American MA was significant $I^2 = 87\%$ and $Tau^2 = 0.006$.

The sub-group combining studies conducted in Europe included data from Finland, Netherlands and Italy (Figure 5). Exposure to treated water in these jurisdictions resulted in a pooled point estimate for reported cancers RI 1.153 (1.049, 1.267) $p = 0.003$. There is statistically significant heterogeneity for this analysis $I^2 = 96\%$ and $Tau^2 = 0.012$. Kukkula (Kukkula and Lofroth 1997) is an outlier with wide CLs but only contributes 3% to the overall point estimate. This MA is dominated by four Finnish studies all by Koivusalo et al. spanning four years from 1994 to 1998. Combined they contribute 70% to the point estimate however with narrower CLs.

In contrast, combining results for studies conducted in Asia: all cancers, Taiwan and China (Figure 6) returned a point estimate for all reported cancers RI 1.119 (0.954, 1.312). It was not statistically significant ($p = 0.167$). Furthermore, the three more recent studies from Taiwan (Chiu et al. 2010; Liao et al. 2012; Tsai et al. 2013) contributing 64% of the weighting may be considered low exposure based on the authors cut off for exposure being 4.9ppb TTHM (Table 2). Individually, the remaining two studies accounted for 35% of the overall point estimate (Tao et al. 1999; Yang et al. 1998) returning a significant association between CDB and reported cancers; however, these studies were conducted pre-year 2000 with potentially higher CDB exposure than the more recent Taiwanese studies. Similar to the North American and Europe MAs, the analysis had statistically significant heterogeneity $I^2 = 71\%$ and $Tau^2 = 0.02$.

Impact of gender, all reported cancers.

Eleven of the 24 studies reported differentiated cancer risk based on being male (Figure 7). For all reported cancers exposure to CDB returned a statistically significant point estimate ($p = 0.005$) demonstrating increased risk RI 1.102 (1.029, 1.179). Heterogeneity is high I^2

= 87% and Tau^2= 0.007. Five studies accounting for 31% of the pooled point estimate had statistically significant ($p < 0.05$) association between CDB exposure and cancer risk. The remaining six studies had risk indices clustered around unity.

Fourteen studies reported on the impact of CDB exposure in females (Figure 8), Table 3. The pooled point estimate for this meta-analysis result is RI 1.062 (1.011, 1.117) and was statistically significant ($p = 0.017$). The heterogeneity for the female sub-group was less than that observed for males however, it remained statistically significant with I^2 = 68% and Tau^2= 0.004. Five of the fourteen studies had a statistically significant ($p < 0.05$) impact of CDB on all reported cancers in females and these contributed 48% towards the point estimate.

CDB Exposure and Cancer Specific Risk.

Of the 27 reported cancers five cancer sites (breast, female reproductive, melanomas, non-Hodgkin's and lung) had statistically significant increased risk due to exposure to CDB (Table 3).

Eight studies reported on the association between CDB exposure and risk of breast cancer (figure 9). The pooled point estimated was statistically significant for breast cancer RI 1.223 (1.086, 1.377) $p = 0.001$. At the level of individual studies, five had a statistically significant increased risk associated with CDB and these contributed 60% towards the overall point estimate. The remaining studies had point estimates close to unity. Further sub-group analysis of female reproductive cancers (ovarian, cervix, corpus luteum and endometrium) demonstrated a statistically significant increase risk RI 1.167 (1.029, 1.324) $p = 0.016$ for these cancers (Figure 10). However, this analysis is dominated by ovarian

cancer (4 studies) and the results for non-ovarian cancers should be considered with caution.

The risk of CDB exposure and non-Hodgkin's lymphoma was evaluated in 5 of the included studies (Figure 11). A statistically significant increased risk for non-Hodgkin's RI 1.309 (1.231, 1.393) p = 0.000 was observed for this sub-group. Statistical heterogeneity was low I^2 = 2% and Tau^2= zero and this low intra- and inter-study variance returned a predictive interval (PI) that did not span unity PI 95%, (1.169-1.467), (Table 3). However, given that two of the five included studies contributed 96% to the pooled estimate the generalization of this result should be considered carefully.

Melanomas (Figure 12) and lung cancer (Figure 13) were reported on five and six of the included studies respectively. Within this data pool both these cancer sites had a statistically significant increase risk on exposure to CDB, melanoma, RI 1.438 (1.027, 2.013) p = 0.034; lung, RI 1.165 (1.092, 1.243) p = 0.000. For both sub-group analyses three individual studies all statistically significant, dominated and contributed 69% and 93% to point estimates for the risk of melanoma and lung cancer, respectively. The remaining studies had risk estimates that clustered around unity. Unlike melanomas the observed intra- and inter- study variance for lung cancer was low I^2 = zero and Tau^2= zero, Table 3 and this low variance also returned a predictive interval that did not span unity 1.063-1.277 (PI, 95%).

Statistical heterogeneity associated with the included meta-analyses.

Measures of heterogeneity are provided in Table 3. With the exception of non-Hodgkin's and lung analyses all meta-analyses had statistically significant heterogeneity. As such, the

point estimates should be considered in light of within and between study heterogeneity. The reporting detail for duration of exposure as well as the level and type of CDB was such that refining sub-group analyses beyond those included was not possible.

Sensitivity Analysis

For all meta-analyses applying the one study removed method demonstrated that no individual study contributed more to the overall result (data not shown).

Publication Bias

Only one meta-analysis had statistically significant publication bias this being all male cancers (data not shown).

Narrative Synthesis

The following cancers, from three included studies were reported once and therefore not meta-analysed; cervical (Wilkins III and Comstock 1981), endometrium (Doyle et al. 1997), corpus luteum, testicular, thyroid and skin cancer excluding basal cell carcinoma (Koivusalo et al. 1997). No significant association of any of these cancers with CDB was reported (Table 3).

One study reporting odds ratio for childhood leukaemia (Infante-Rivard et al. 2001) was excluded because varying exposures to THM percentiles were compared. Odds ratios were close to unity and CLs spanned unity when comparing average exposure levels less than the 95th percentile with equal to or greater than the 95th percentile of THM level.

Four studies reported results as correlation coefficients with *p* values and therefore could not be included in MA (Cantor et al. 1978; Flaten 1992; Foster et al. 1997; Kool et al.

1981). These studies represented four countries, England, US, Norway and the Netherlands. The US study (Cantor et al. 1978) used the 1960 population as the standard (181 million people) and the Netherlands study (Kool et al. 1981) included approximately one third of the Dutch population (or 4.6 million people). All four studies reported statistically significant positive associations across a range of cancers and both genders including malignant melanoma, leukaemia, buccal cavity/pharynx, liver, lung, brain, kidney, and non-Hodgkin's lymphoma in addition to bladder and colorectal cancers. Three of the four reported on multiple cancers and the fourth reported only on leukaemia (Table 2).

Cantor (Cantor et al. 1978), excluding bladder cancer results reported significant correlations between CDB exposure and kidney cancer ($r = 0.42$, $p = 0.04$) in the male cohort where 85-100% of the population were served chlorinated water, and non-Hodgkin's lymphoma for women who resided in the mountain pacific region ($r = 0.87$, $p = 0.01$). For all other cancers reported by Cantor, results are non-significant and direction of correlation coefficient varied.

Flaten (Flaten 1992) reported significant correlation coefficients for all cancer sites combined for both men ($r = 0.59$, $p = 0.005$) and women ($r = 0.80$, $p = 0.0001$). Malignant melanoma was also significantly correlated for both men and women in the positive direction. In contrast, for stomach cancer in both men and women, significant negative correlations were reported. Excluding colon, rectum and bladder this study reported on an additional 12 cancer sites of which trachea, bronchus, lung, breast, and uterine cervix also had statistically significant correlations. For men, excluding cancers of the colon, rectum and malignant melanoma, eight additional cancer sites were assessed returning a

statistically significant positive correlation for cancers of the buccal cavity/pharynx. Although 15 variables were used in the correlation and multiple linear regression analysis, smoking as a co-variable was not included in this study. Foster et al. (Foster et al. 1997) reported on leukaemia's across all ages against water quality variables including THM. Leukaemia's were subdivided into six haematological malignancies (leukaemia's). Four of the six returned significant correlation coefficients to THM. Three were positive associations with correlation coefficients of 0.35-0.38. One negative correlation was reported for chronic myeloid leukaemia (CML) -0.37. All were significant at $p < 0.05$. In addition to colon, rectum and bladder Kool et al. (Kool et al. 1981) assessed a further four cancer sites these being the oesophagus, stomach, liver and lung. Standardized mortality rates were assessed against THM and aside from lung cancer in females, all were positive correlations; however, these only reached statistical significance ($p < 0.05$) for oesophageal (r =0.60) and stomach (r = 0.46) cancer sites in males.

Three studies all from North America, (two from the US and one from Canada) reported their results based on regression analysis (Carlo and Mettlin 1980; Clark et al. 1986; Wigle et al. 1986). Due to differences in the regression models, results were not subjected to meta-analysis. All three studies reported statistically significant associations across a range of cancers including stomach, colorectal, gastrointestinal tract, urinary tract and pancreas (Table 2).

Clark's (Clark et al. 1986) results are based on the national organics reconnaissance survey for halogenated organics in the US (Symons et al. 1975). Seven cancers excluding large intestine, rectum and bladder were assessed for men and women against surrogate markers for CDB (Carbon Chloroform Extract, CCE and Carbon Alcohol Extract, CAE) showing

significant regression results ($p < 0.01$) for men, oesophageal ($R^2 = 0.177$), stomach ($R^2 = 0.096$), liver ($R^2 = 0.021$) and lung ($R^2 = 0.064$). For women, stomach ($R^2 = 0.109$), lung ($R^2 = 0.027$) and breast ($R^2 = 0.081$) were reported as statistically significantly regressed to CDB exposure ($p < 0.01$).

A second study by Carlo and Metlin, (Carlo and Mettlin 1980) evaluated THM exposure against age adjusted cancer incident rates for whole population as well as separate analyses of males and females. Three cancer sites excluding colon, rectum and bladder were assessed; oesophagus, stomach and pancreas. No significant regressions were observed for the total population. The only statistically significant result was the correlation of CDB exposure with pancreatic cancer in white males ($r = 0.16$, $p < 0.05$). The final included study reporting regression results was by Wigle et al. (Wigle et al. 1986). These authors reported on ten cancers (Table 2), excluding large intestine and bladder. Standardized mortality rates for the total population as well as male and females were assessed against THM and chloroform. In this study, the application of multiple regression did not demonstrate any significant association between THM or chloroform and the standardized mortality rate.

One study from Iowa in the US reported results as incident rates; however, this was excluded from MA because it did not disclose chlorine use or any CDB exposure indices instead relying on well depth, ground or surface water as the exposure agent (Bean et al. 1982). Four cancers (prostate, breast, stomach and lung) in addition to those of the rectum, colon and bladder were assessed. Significantly higher incidence of lung cancer was reported for both men and women for surface water compared with ground water ($p < 0.01$). Men increased by 125% and women by 115% as population density increased from

cohorts of 1000-10,000 to population cohorts exceeding greater than 50,000. Importantly, smoking was accounted for as a confounder in this study. Water source is used as a surrogate for CDB content with ground water typically containing less organic matter than surface water and not subjected to chlorination resulting in little or no CDB. The results are potentially confounded since ground water is susceptible to industrial pollutants. Furthermore, Bean et al. reported that wells less than 150 feet in depth (46 m) were found frequently to contain elevated nitrate levels suggesting a potential contamination from surface run off (Table 2).

Discussion

Exposure to CDBs is now considered widespread (Villanueva et al. 2015) and current global rates of cancer incidence and mortality are considered to be at epidemic proportions (American Cancer Society 2016; Servan-Schrieber 2016). It has been more than 40 years since Rook (Rook 1974) first identified THMs in public drinking water supplies correlated with increased cancer rates in the US. Villanueva et al., (Villanueva et al. 2015), Hrudey and Fawell, (Hrudey and Fawell 2015) and Grellier (Grellier et al. 2015) have published reviews that attempt to summarize the current knowledge base. Hrudey and co-workers have recently reviewed the association with bladder cancer in detail (Hrudey et al. 2015). Meanwhile, the US EPA, who leads the world in regulatory legislation and oversight of CDBs continues to proactively regulate the chlorine disinfection process in an effort to mitigate potential public health risks, the most serious identified including cancers and pregnancy complications (Tomasz 2009; USEPA 2015). The WHO and other countries around the world are following the lead of the US (World Health Organization 2007).

This systematic review is the first to comprehensively review and meta-analyse the body of evidence accumulated since 1974 for possible associations between CDB and cancers other than bladder or colorectal and helps fill an important knowledge gap. The CDB public health story continues to evolve as a result.

Overall, our results expressed in percentages demonstrated a statistically significant relative risk of 13% (95% CI; 7%, 19%) for all reported cancers (all geographical regions, both genders but excluding bladder or colorectal cancers) being associated with usage of water that has been chlorine treated and containing CDBs. Global estimates of absolute cancer incidence and mortality are 182 and 102 per 100,000 population, respectively (IARC 2014). An estimate of the absolute reduction in cancer incidence and mortality by avoiding CDB exposure can be calculated. Based on our results, the estimate of absolute reduction in cancer incident for all reported cancers is 24 / 100,000 population with a range of 13 to 35 / 100,000 population and estimated absolute reduction in cancer mortality is 13 / 100,000 population with a range of 7 to 19 / 100,000 population (Table 4). Furthermore, the range of absolute effect in cancer incidence and mortality for all reported cancers and geographical regions is 1% (Female: all cancers) to 31% (Asia: all cancers) and for specific cancers 3% (Female Reproductive and Melanoma) to 113% (Melanoma) (Table 4).

These values are in line with those published by Malcolm and co-workers, using the relative risk range of 1.3 - 1.5 (Cantor 1994) which derived a population attributable risk (PAR) for the burden of morbidity and mortality from cancers of bladder, colon and rectum in New Zealand (Malcolm et al. 1999). From a predicted mortality PAR, 25% of cancers could be prevented by eliminating CDB exposure, or 139 – 329 preventable deaths

in 1995 from an estimated population of 2.4 million with a known exposure to CDBs. This converts to 6 – 14 / 100,000 population for bladder, colon and rectum in New Zealand.

The statistically significant results we report for specific cancers reflect the leading global cancer incident statistics. Breast, female reproductive, melanoma and lung all rank in the top five cancers globally. The association between these cancers and CDB exposure adds to the existing data for bladder and colorectal cancers, and together are a cause for concern that CDB exposure is an environmental risk for these cancers (IARC 2014).

In addition, the significant results returned for melanoma and lung cancers raises the question of whether CDB exposure plays an important and heretofore unrecognized role in these cancers. Certainly, it is now recognized that dermal and inhalation exposure to CDBs is significant and may be more important than ingestion as exposure routes (Villanueva et al. 2007); however, the mechanism of cancer initiation and role of varying exposure routes whereby CDBs enter the body is yet to be understood.

The USEPA through its Integrated Risk Information System (IRIS) (USEPA 2005a) programs continues to seek answers and develop risk models for environmental risk factors for adverse health effects, including cancers. Indeed, the US Health and Environmental Research Online (HERO) database lists 850 studies assessing the cellular toxicity of CBDs between 1996 and 2014 (USEPA 2016c). Of these, some 160 were on human cell cultures. However, to develop an informed risk assessment of the health consequences of CDB exposure, the specific characteristics of the region must be clearly defined and understood as the macro flora, fauna, geophysical properties and anthropological development of agriculture, industry and urbanization will vary by location and season (Malcolm et al. 1999). Taking such factors into account, a risk model will be adjusted for all sources of

organics in the water and ultimately the chemical profile of source water as it is collected for water treatment. Such variations in the organic profiles of source water pre-treatment will influence the final profile of disinfection by-products post-treatment and is further compounded by the type of water disinfection process applied with chlorine, chloramine, chlorine dioxide, ozone, UV etc., and combinations of these each creating unique suites of disinfection by-products (Richardson et al. 2007).

The observed variation in cancer incidence and mortality associated with CBD exposure reported over the past 40 years may be partially explained by the heterogenic nature in each of these water quality variables, which in turn creates unique CDB profiles for each geographical region (Richardson and Postigo 2012). The challenge is assessing the multitude of mixtures especially given that over 600 unique chemical signatures have been identified, but are still to be chemically characterized. The relative toxicities of CDB mixtures are unknown as well as how they change over time or are affected by anthropological inputs. In addition, distinct populations each with unique lifestyle factors as described by Villanueva (Villanueva et al. 2015) and Hrudey (Hrudey et al. 2015; Hrudey and Fawell 2015), with unique genotypes and susceptibility to CDB exposure and cancer contributes additional layers of confounding in studies from around the world, and may explain why such variability within and across studies over time has been observed. Furthermore, Hrudey (Hrudey et al. 2015) reports an exposure level effect for bladder cancer from Villanueva's 2007 bladder cancer study (Villanueva et al. 2007). With increasing exposure, the risk measure increased; however, the risk measure for a given exposure to CDB may not be statistically significant, but over multiple exposure levels there is a statistically significant positive trend line. A similar trend is noted in Cantors results (Cantor et al. 1978).

Chlorine and disinfection dosing patterns within water treatment plants have also changed over the past 40 years, as the knowledge base has grown and the public health consequences of CDB exposure has been explored. As a result, many countries are either actively regulating to lower or restrict CDB levels or recommend best practice guidelines (USEPA 1975, 2005a, 2006b, 2015; WHO 2007). This trend has altered the exposure indices data used to assess cancer outcomes over time, adding yet another variable that must be considered to fully comprehend the dynamic nature of CDB exposure and any underlying relationship to cancer.

Clark and co-workers documented the increasing global organic chemical burden over the last century and quotes a 10-fold increase from 5 billion to 50 billion tonnes per year in the "chemical revolution" that occurred in the 30-year period between the years of 1956 and 1986 (Clark et al. 1986). More recently new and emerging contaminants such as endocrine disruptors, pharmaceutical and personal care products, mixtures of organic chemicals, perfluorinated chemicals and nanoparticles influencing water quality have become a concern and can confound study results further, if not accounted for in the study design (Richardson et al. 2007).

The points above help to explain the variance in regional, geographical, gender and range of specific cancer results associated with CDB exposure that have been reported over the past 40 years, both within individual studies reviewing multiple cancers as well as across studies.

This heterogeneity is reflected in the result of our meta-analysis, and can be explained in this way as the statistically significant results we report, with the exception of two (non-

Hodgkin's and Lung each have significant predictive intervals) all show high heterogeneity within and across studies. However, for both non-Hodgkin's and lung cancer, the studies by Koivusalo dominate the point estimate. Two of these (Koivusalo et al. 1995; Koivusalo et al. 1997) contribute 96% to the point estimate for non-Hodgkin's (Figure 11), and the 1997 study contributes 73% to the point estimate for lung cancer (Figure 13). One explanation for this dominance may be related to the exposure index used by Koivusalo, who in each of his studies, used mutagenicity to assess exposure to CDB. Mutagenicity may provide a more comprehensive and accurate surrogate measure of potential adverse water quality and exposure than more commonly used exposure indices such as TTHM or chloroform, which do not reflect the true complexity of the CDB profile and potential toxicity. However, the correlation of mutagenicity with CDBs profile or content needs to be developed to confirm the effect is from CDBs and not some other constituent. Such research would also confirm the veracity of mutagenicity as a suitable exposure index for CDB. Use of human cell cultures paired with mutagenicity testing may be one way to improve exposure indices reporting and assess risk.

The understanding of the potential toxicity of any given mixture of CDBs can be more closely assessed if the CDB profile or signature is known. Knowledge of how these change over time, or how they are affected by anthropological inputs is also required. This does not require identification of individual chemicals but rather profiles of the chemical signatures. Application of such profiles will inform on the organic chemical diversity in water, thereby allowing them to be correlated to incident and mortality date or to laboratory test of toxicity. This should improve the accuracy of risk modelling.

Moving forward the question might be “How pure should our water be?” or, “What water quality (qualities) best support (s) human health and hydration?” Malcolm states in 1999 “it is time to go beyond the assumption that we must simply accept the risks of CDBs because they are balanced against the much greater risk of water-borne infectious diseases. Microbiological and chemical safety are not mutually antagonistic aims” and goes on to claim “the cost of actions taken to decrease CDBs must be weighed against the financial, health, and social costs of the (adverse) health effects of CDBs and not against the cost of water-borne disease prevented by disinfection”, (p.407, Malcolm et al. 1999). Although the ability to accurately define a causal agent is almost impossible because of the number of variables involved the need for agreement on research priorities and translation of these results into public health management should be the priority. In addition to improving water source purity (quality) and treatment plant procedures to reduce CDBs, purification of water at the point-of-use remains an important and viable way for consumers to reduce exposure to CDBs and other potentially toxic chemicals in water.

Limitations of Systematic Review.

Limitations of this systematic review fall into two categories and are related to heterogeneity of reported data and publication bias (male all cancers only). Ultimately the decision to combine data sets from twenty-four studies out of thirty-three accepted into this systematic review, reveal the decision to accept this limitation and proceed with meta-analysis.

For many cancer sites there were limited numbers of peer reviewed publications. Attempts to ameliorate this risk included the use of the Joanna Briggs Institute (JBI) CReMS (Comprehensive Review Management System) Quality Assessment and MAStARI

(Supplemental Material Appendix 2), and inclusion of literature derived from grey literature searches.

A limitation of the data synthesis is the reliance on observational studies, which limits the ability to draw causal inference. This is compounded by the lack of detail as to how confounders for statistical correction were selected in the epidemiological studies in the current literature. Similarly, detail regarding the process of control matching in the case control literature was also lacking. These deficiencies are a reflection of the time when these studies were conducted. Any reanalysis of existing published data sets or new studies should employ statistical methods that increase the power of non-randomized control designs to infer causality. Emerging statistical methods include the use of Direct Acyclic Graphs (DAGs) (Weisskopf et al. 2015) and propensity scores (Austin 2011). Applying DAGs ensure that key confounders are appropriately selected and controlled to improve true exposure and response relationships are analysed in epidemiological studies. For case control studies the application of propensity scores has been proposed to improve the matching of cases with controls (Austin 2011). Methods such as these allow researchers to move closer to causality inferences when randomized control trials study designs are impossible for ethical reasons, or impractical due to data structure.

A meta-regression would have been the ideal synthesis. However, this was not possible because of the major limitation in determining exposure to CDBs and risk of cancers. In many cases, exposure levels have been generated from retrospective data based on the limited monitoring of a single CDB in the water. Given the complexity in CDB exposure that is likely to exist, with each profile having a unique toxicity profile, the lack of clarity in exposure indices introduced a degree of uncertainty within the results, further confounded by reporting of different CDBs as the exposure indices. To address these

difficulties, only measures of risk for confirmed exposure to CDB, chlorinated surface water or mutagenicity were combined in our analysis. While this provided an overview of the potential cancer risk, it does not provide any information on which CDBs, or profile of CDBs are of concern and the level that can be considered safe. Other researchers have attempted to review the literature and made the same observation that sufficient detail on CDB exposures is lacking in the current literature base (Grellier et al. 2015; Hrudey and Fawell 2015).

Conclusion

The result of the meta-analyses demonstrated that exposure to chlorine treated water or water with a known mutagenicity resulted in an overall relative increased risk of cancer by approximately 13%. This increased risk is for those cancers reported in the literature and pooled across all geographical regions and for both genders. For specific cancers, statistically significant point estimates were derived for breast, female reproductive, melanoma, non-Hodgkin's and lung. Non-Hodgkin's and lung cancer have significant predictive intervals. These results reflect the top reported cancers globally, and provide evidence in support of the association between CDB and cancer, strengthening the possibility that this relationship could be causal. Our results do affirm and add to the evidence established for bladder and colorectal cancers. However, the high degree of heterogeneity consistently observed both within and across studies over the last 40 years prevent making this a definitive conclusion. Heterogeneity within and across studies remains a feature of the research into CDBs and risks to health and is explained by the many variables. Researchers have attempted to account and adjust for confounders. There are potentially many that remain unidentified and contribute to the difficulty in elucidating consistent patterns of cancer incidence and mortality.

Given the complexity of environmental exposures attempts to identify the causal agents will have limited return. The issue is establishing or refining risk assessment models for practical application in the field. Our results support the findings of the US EPA and their ongoing decisions to reduce exposure to CDBs (USEPA 2015). The objective is the provision of safe water to the end user; as such, consideration of health risks beyond infectious agents should be a public health concern. This extension should include all water uses given the significance of dermal and inhalation routes for CDB exposure.

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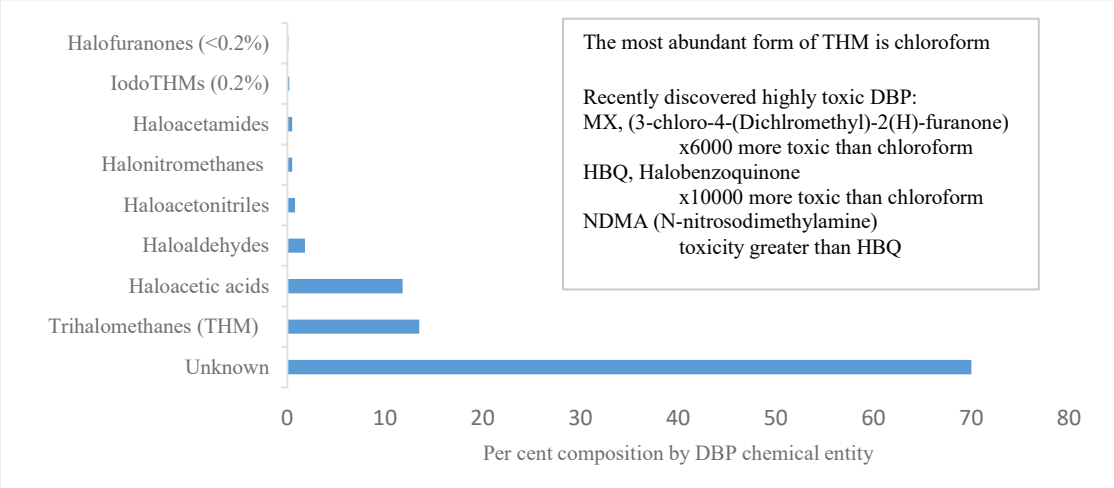


Figure 1: Percentage of Total Organic Halogen (TOX) accounted for by Quantified Disinfection By-products. (Richardson and Postigo 2012)

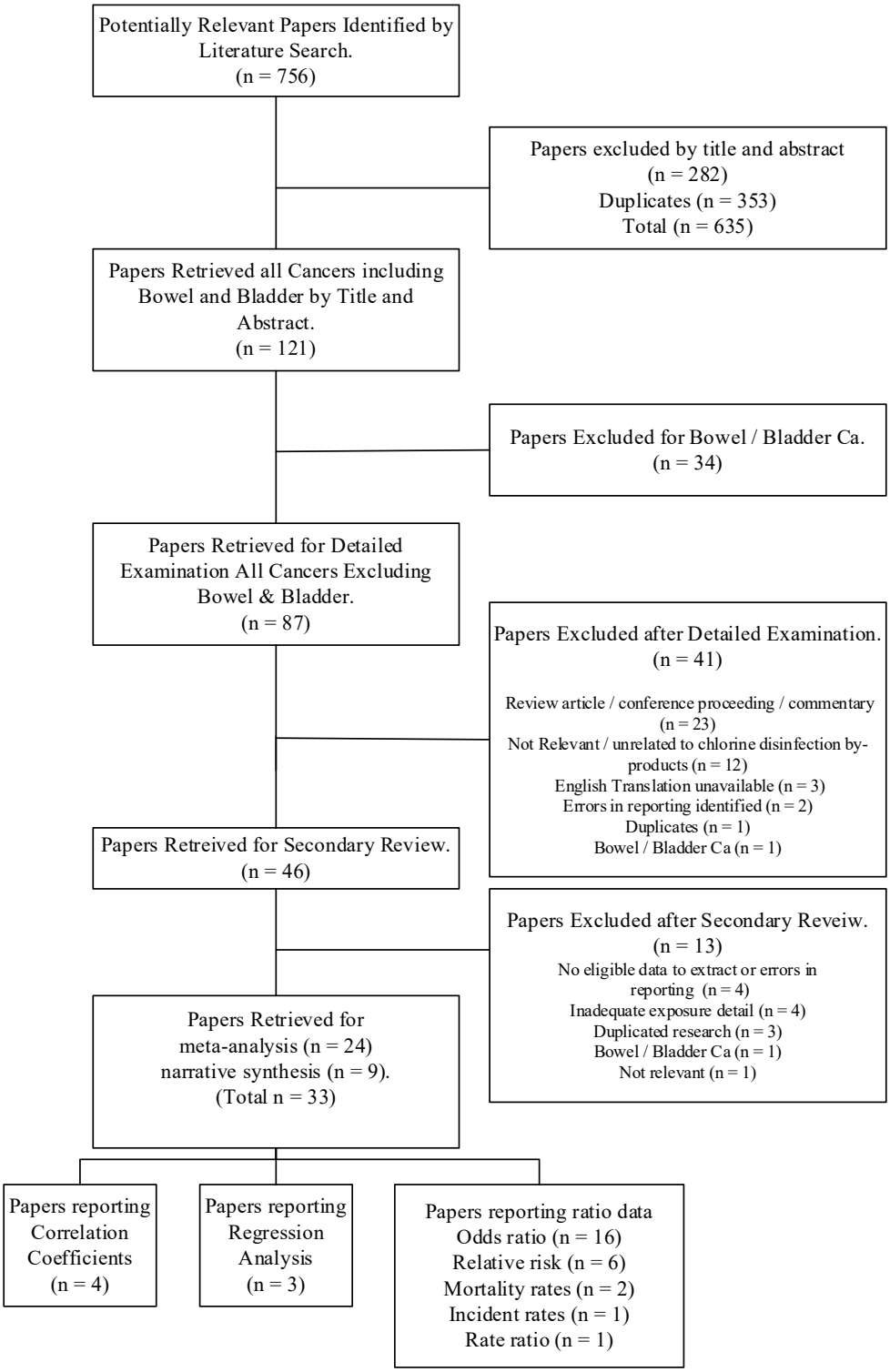
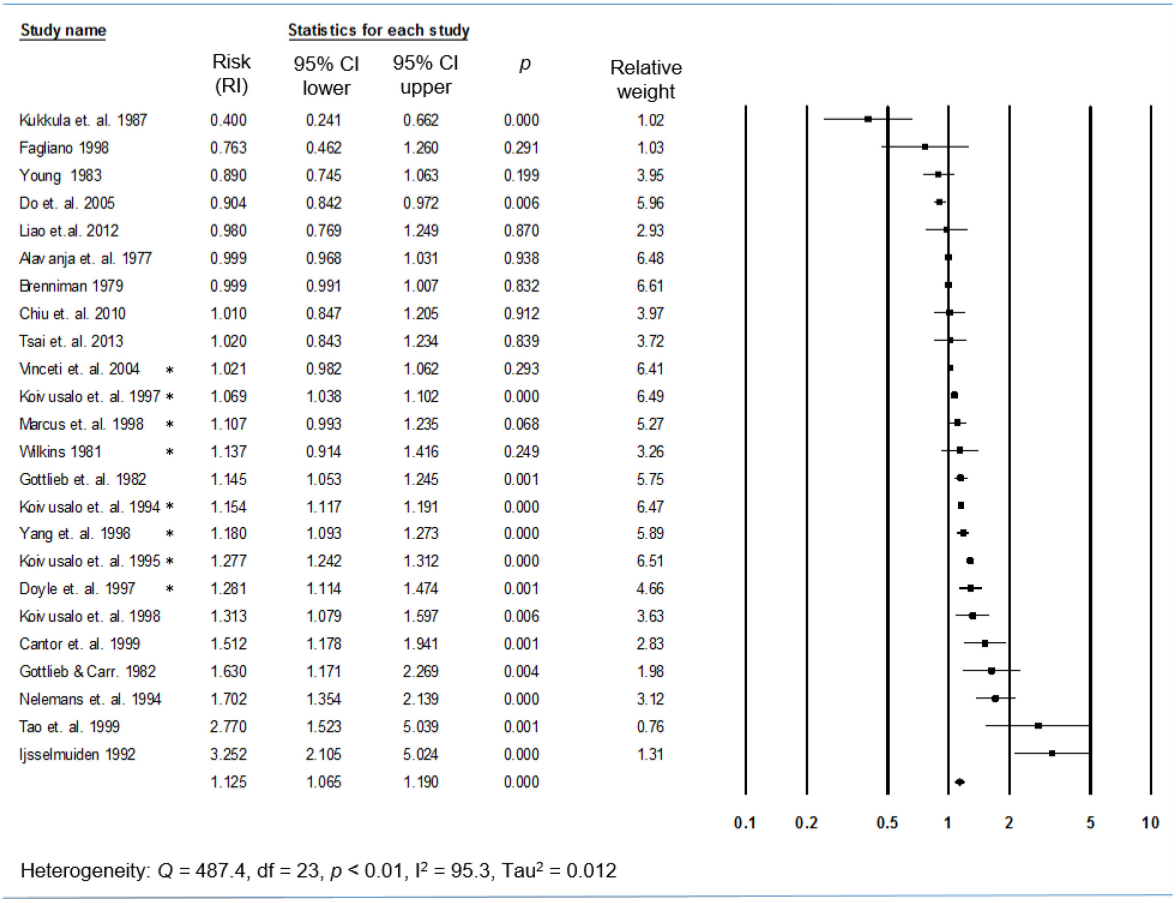


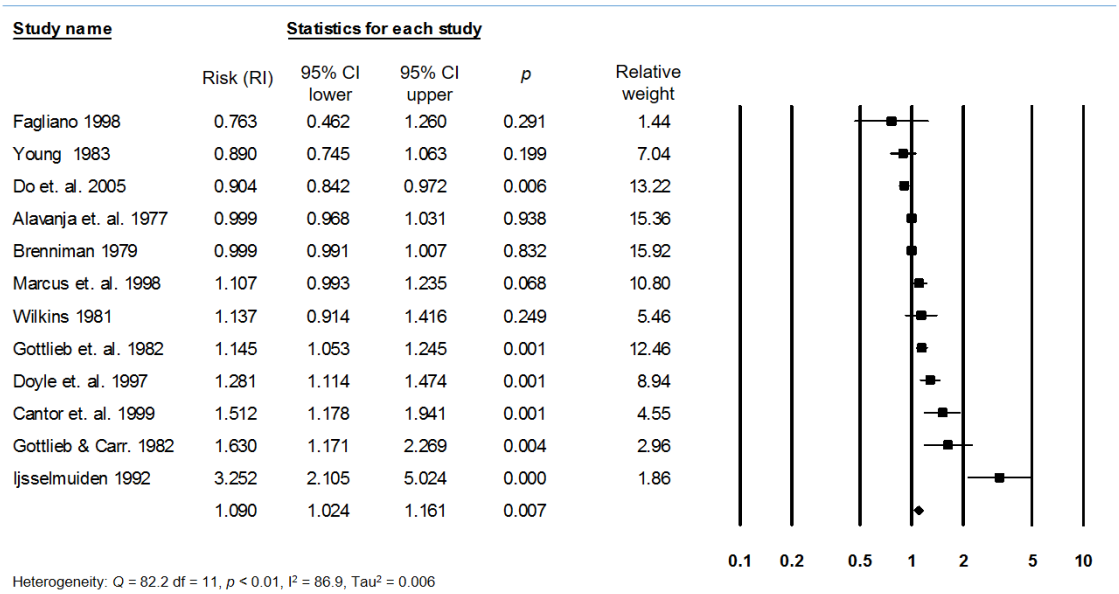
Figure 2: Flow chart and article selection.



Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Kukkula et. al. 1987	0.400	0.241	0.662	0.000	1.02
Fagliano 1998	0.763	0.462	1.260	0.291	1.03
Young 1983	0.890	0.745	1.063	0.199	3.95
Do et. al. 2005	0.904	0.842	0.972	0.006	5.96
Liao et.al. 2012	0.980	0.769	1.249	0.870	2.93
Alavanja et. al. 1977	0.999	0.968	1.031	0.938	6.48
Brenniman 1979	0.999	0.991	1.007	0.832	6.61
Chiu et. al. 2010	1.010	0.847	1.205	0.912	3.97
Tsai et. al. 2013	1.020	0.843	1.234	0.839	3.72
Vinceti et. al. 2004 *	1.021	0.982	1.062	0.293	6.41
Koivusalo et. al. 1997 *	1.069	1.038	1.102	0.000	6.49
Marcus et. al. 1998 *	1.107	0.993	1.235	0.068	5.27
Wilkins 1981 *	1.137	0.914	1.416	0.249	3.26
Gottlieb et. al. 1982	1.145	1.053	1.245	0.001	5.75
Koivusalo et. al. 1994 *	1.154	1.117	1.191	0.000	6.47
Yang et. al. 1998 *	1.180	1.093	1.273	0.000	5.89
Koivusalo et. al. 1995 *	1.277	1.242	1.312	0.000	6.51
Doyle et. al. 1997 *	1.281	1.114	1.474	0.001	4.66
Koivusalo et. al. 1998	1.313	1.079	1.597	0.006	3.63
Cantor et. al. 1999	1.512	1.178	1.941	0.001	2.83
Gottlieb & Carr. 1982	1.630	1.171	2.269	0.004	1.98
Nelemans et. al. 1994	1.702	1.354	2.139	0.000	3.12
Tao et. al. 1999	2.770	1.523	5.039	0.001	0.76
Ijsselmuiden 1992	3.252	2.105	5.024	0.000	1.31
	1.125	1.065	1.190	0.000	

Heterogeneity: $Q = 487.4$, df = 23, $p < 0.01$, $I^2 = 95.3$, $Tau^2 = 0.012$

Figure 3: All reported cancers, impact of exposure to chlorine disinfection by-products on incidence and mortality risk (both sexes and all geographical regions). The * indicates cohort studies. All remaining studies were of a case control design.



Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Fagliano 1998	0.763	0.462	1.260	0.291	1.44
Young 1983	0.890	0.745	1.063	0.199	7.04
Do et. al. 2005	0.904	0.842	0.972	0.006	13.22
Alavanja et. al. 1977	0.999	0.968	1.031	0.938	15.36
Brenniman 1979	0.999	0.991	1.007	0.832	15.92
Marcus et. al. 1998	1.107	0.993	1.235	0.068	10.80
Wilkins 1981	1.137	0.914	1.416	0.249	5.46
Gottlieb et. al. 1982	1.145	1.053	1.245	0.001	12.46
Doyle et. al. 1997	1.281	1.114	1.474	0.001	8.94
Cantor et. al. 1999	1.512	1.178	1.941	0.001	4.55
Gottlieb & Carr. 1982	1.630	1.171	2.269	0.004	2.96
Ijsselmuiden 1992	3.252	2.105	5.024	0.000	1.86
	1.090	1.024	1.161	0.007	

Heterogeneity: $Q = 82.2$ df = 11, $p < 0.01$, $I^2 = 86.9$, $Tau^2 = 0.006$

Figure 4: All reported cancers (North America), impact of exposure to chlorine disinfection by-products on incidence and mortality risk

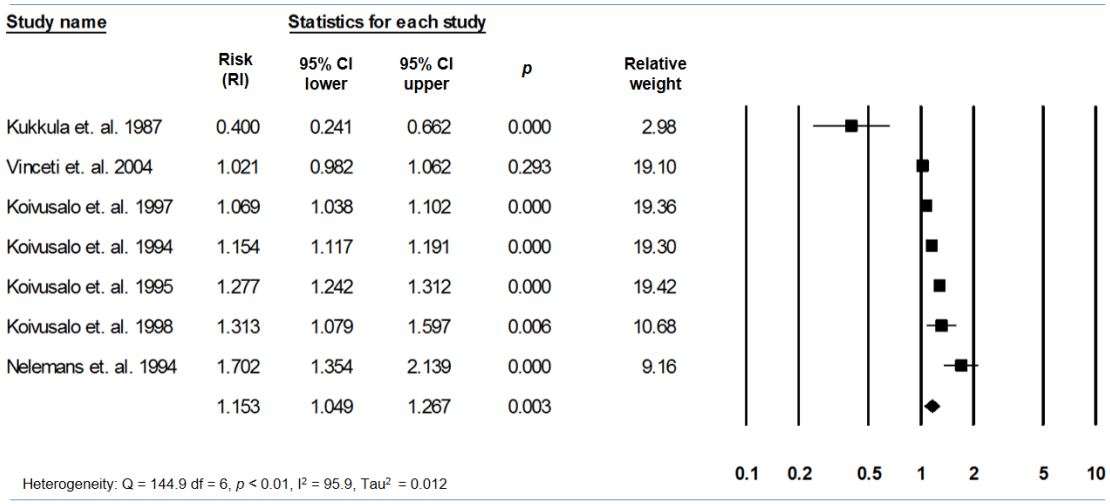


Figure 5: All reported cancers (Europe), impact of exposure to chlorine disinfection by-products on incidence and mortality risk

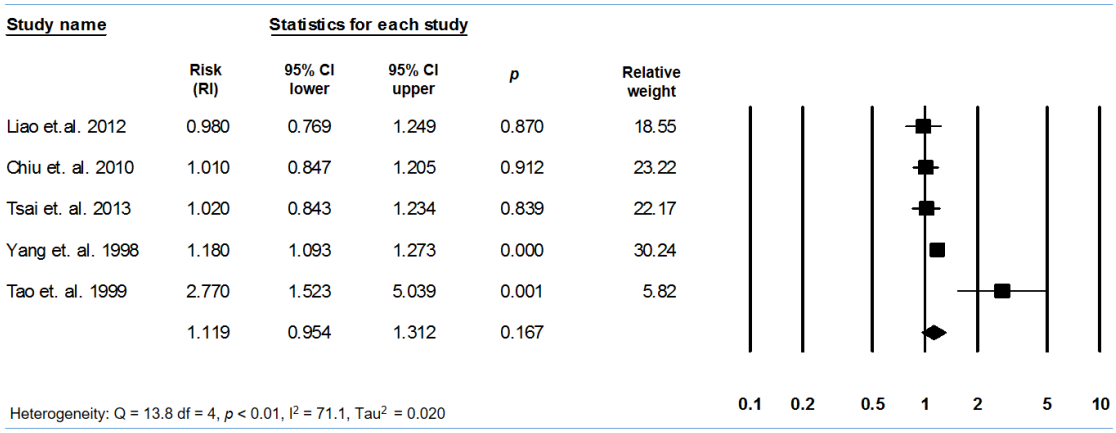


Figure 6: All reported cancers (Asia), impact of exposure to chlorine disinfection by-products on incidence and mortality risk (both sexes and all geographical regions)

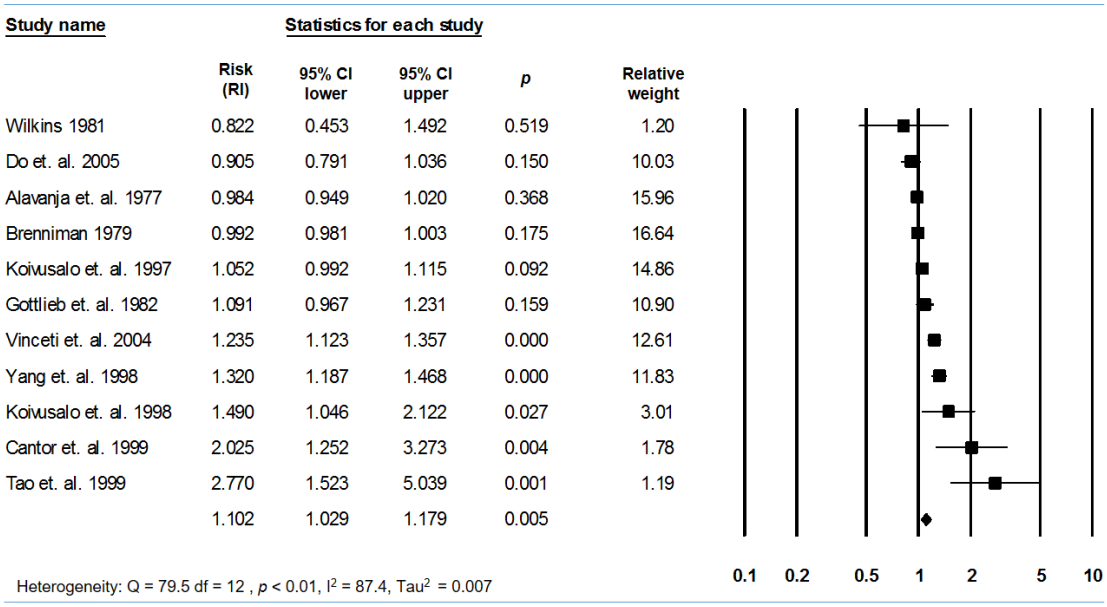


Figure 7: All reported cancers (Males), impact of exposure to chlorine disinfection by-products on incidence and mortality risk

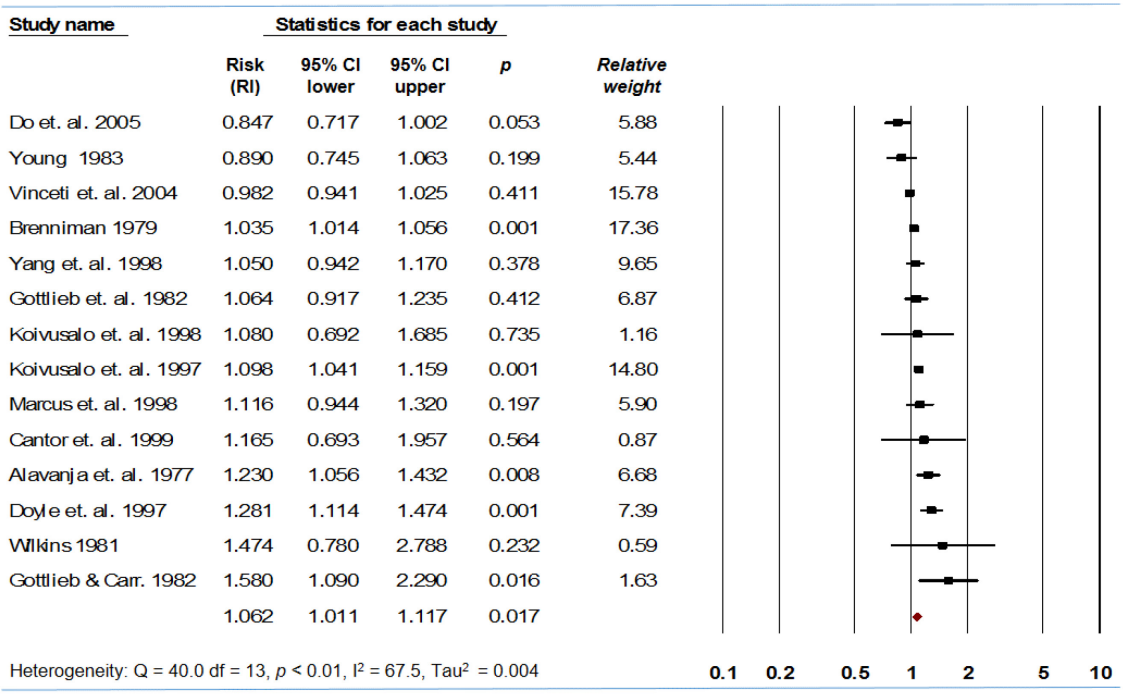


Figure 8: All reported cancers (Females), impact of exposure to chlorine disinfection by-products on incidence and mortality risk

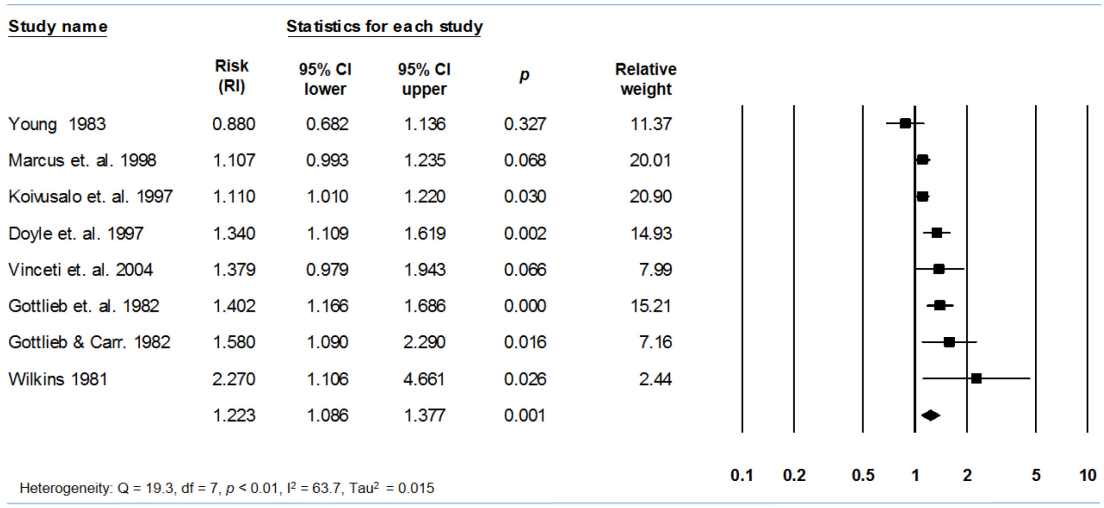


Figure 9: Breast cancer, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

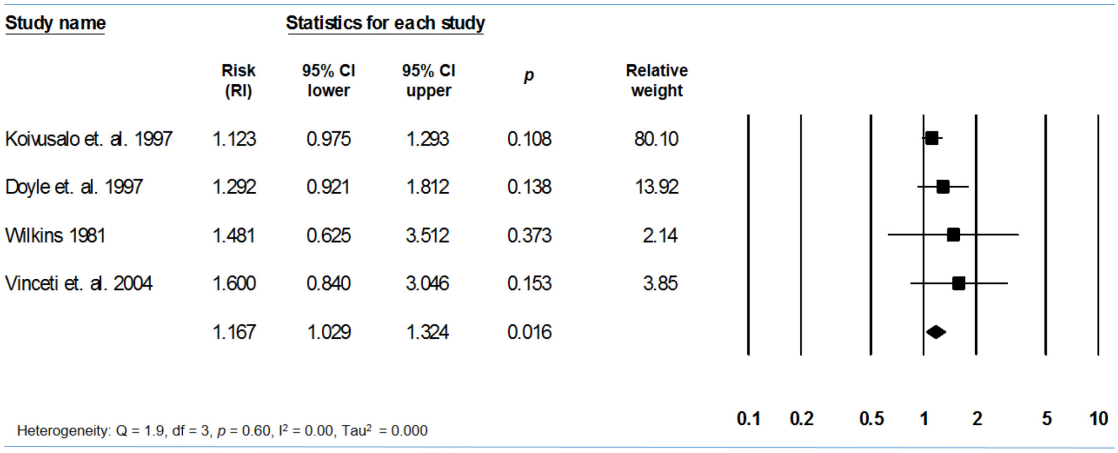


Figure 10: Cancers of the female reproductive tract, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

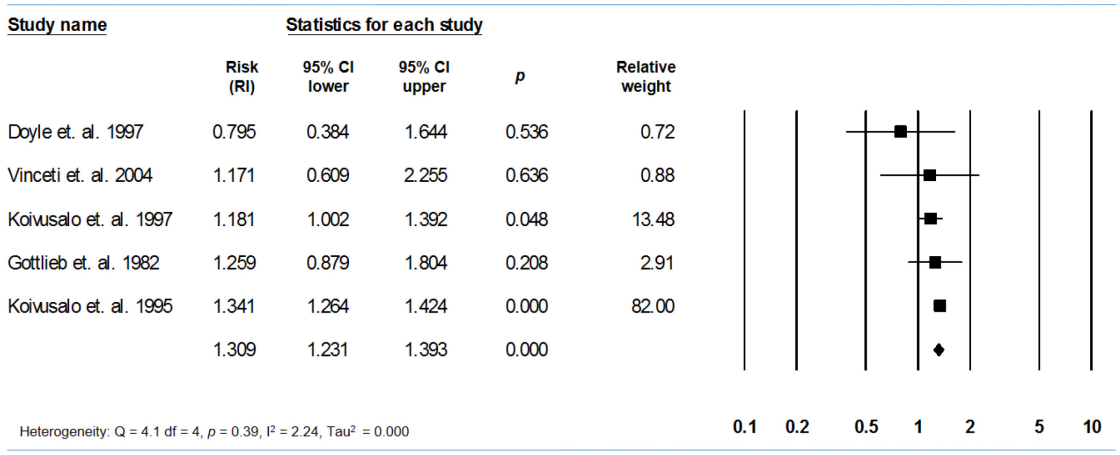


Figure 11: Non-Hodgkin's lymphoma, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

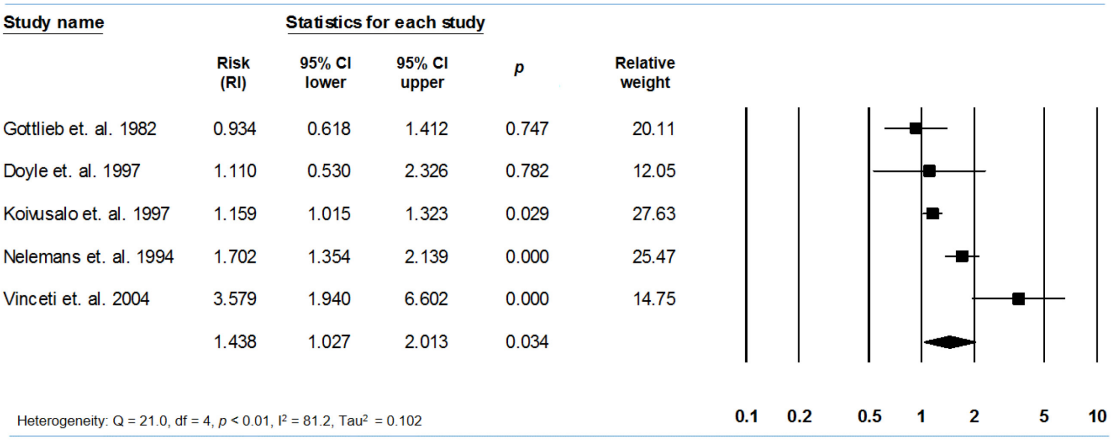


Figure 12: Melanomas, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

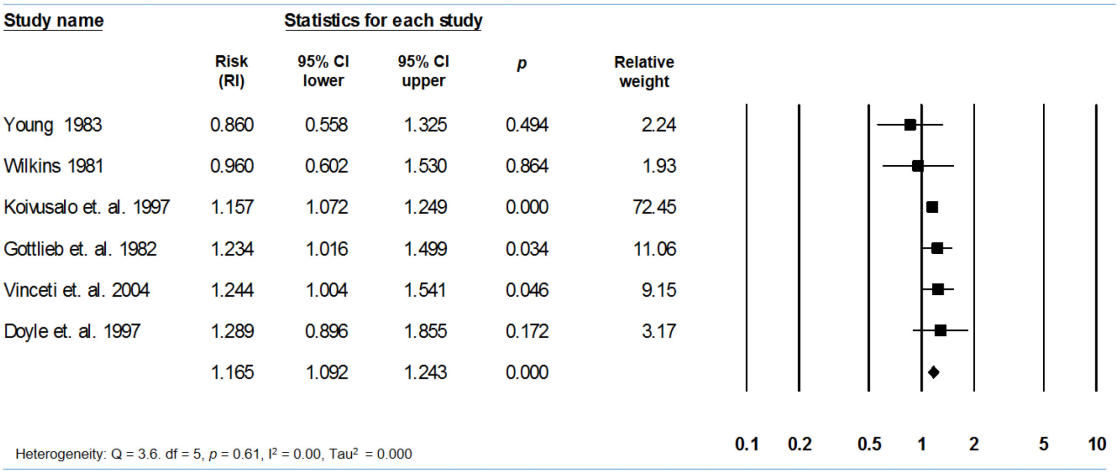


Figure 13: Lung cancer, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Table 1 Eighteen exposure indices used in the 33 included studies. *

Exposure Indices (chlorinated water)		Number of Studies	Study	Reported Range (where available) µg/l (= ppb)
1.	Time	2	Cantor et al. 1999, Gottlieb et al. 1982	
3.	Dose & Time	6	Kiovusalo et al., 1998, Kukkula 1997, Nelemans et al., 1994, Ijsselmuiden et al., 1992, Young 1983, Infante-Rivard et al., 2001	
4.	Chlorinated Water vs. Non Chlorinated Water	7	Kukkula 1997, Nelemans et al., 1994, Alvanja et al., 1978, Wilkins III & Comstock 1981, Flaten 1992, Kool et al., 1981, Yang et al.,1998	
5.	Polluted Water vs. Non-Polluted Water	1	Nelemans et al., 1994	
6.	Ground Water vs. Surface Water	8	Alvanja et al., 1977, Doyle et al., 1997, Wilkins III & Comstock 1981, Kool et al., 1981, Carlo & Mettlin 1980, Bean et al., 1982, Gottlieb et al. 1982, Gottlieb & Carr 1982	
7.	Well Depth	1	Wilkins III & Comstock 1981	
8.	Chlorinated Ground Water vs. Non-chlorinated Ground Water	2	Brenniman et al., 1979, Gottlieb & Carr 1982	
9.	Chlorine Dose and/or Chlorine Residual	3	Young 1983, Gottlieb & Carr 1982, Wigle et al.1986	
10.	TTHM (Total Trihalomethanes) Chloroform* (*Trichloromethane) Bromdichloromethane Dibromochloromethane Bromoform	12	Tsai et al., 2013, Liao et al., 2012, Chiu et al., 2010, Do et al., 2005, Fagliano 1998, Foster 1997, Cantor et al. 1978, Wigle et al., 1986, Carlo & Mettlin 1980, Vincenti 2004, Marcus 1998, Infante-Rivard et al. 2001	0 – 246* ug/l (ppb) * Foster 1997

Table 1 continued

Exposure Indices (chlorinated water)		Number of Studies	Study	Reported Range (where available) µg/l (= ppb)
11.	Chloroform* (*Trichloromethane)	6	Do et al., 2005, Ijsselmuiden et al., 1992, Infante-Rivard et al. 2001, Doyle 1997, Cantor et al. 1978, Wilkins III & Comstock 1981	< 3* – 287** µg/l (ppb) *Do et. al., 2005, ** Doyle 1997
13.	Dibromochloromethane	1	Infante-Rivard et al. 2001	Value at cut off 4.2 µg/l (ppb)
14.	Bromoform	1	Infante-Rivard et al. 2001	Value at cut off 0.66 µg/l (ppb)
15.	BTHM (Brominated Trihalomethanes) Bromdichloromethane Dibromochloromethane Dibromochloromethane	1	Cantor et al. 1978	0.5 – 1.0 umoles BTHM/litre
16.	Mutagenicity	5	Kiovusalo et al., 1998, 1997, 1995, 1994, Tao et. al., 1999	0 - >2,500 net rev/ l and 3,000 net rev / l (high)
17.	Mutagenicity and Chlorinated vs. non-chlorinated water	1	Tao et. al., 1999	3,000 net rev / l (high)
18.	Carbon Alcohol Extract (CAE) & Carbon Chloroform Extract (CCE)	1	Clark et. al., 1986	

Table 2 Characteristics of the 33 studies included in the systematic review.

Included /Excluded in MA (Meta-Analysis)		Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
Studies reporting Odds Ratios (n=16) are all Case Control studies. (Total case control studies n=17)								
1	MA	Alvanja et al. (1978)	USA (New York) 1968-1970	3446 ca mortalities matched with 3444 matched controls from 1.8 million people New York State in 1970	1.8	GI & Urinary tract [Mortality]	Y for both GI and Urinary tract	***Chlorinated vs Non Chlorinated***, surface vs ground and 3 regions to compare organic matter or water source for lung Yes/no for all other cancers stratified by sex
2	MA	Cantor et al. (1999)	USA (Iowa) 1984-1987	375 newly diagnosed brain ca histologically confirmed matched 2,434 controls from approx. 1.94 million people (population of Iowa 1980)	1.94	Brain [Incident]	Y significant result is in the time trend for exposure	***Time***/dose exposure 4 levels 0, ***1-19, 20-39, >=40 yrs.*** D >38 µg/l THM surface water 1.7 µg/l THM chlorinated ground water
3	MA	Chiu et al. (2010)	Taiwan 1998-2007	1056 pancreatic cancer deaths from 65 of 365 municipalities	?	Pancreatic [Mortality]	N	**TTHM** ppb range no specific number <4.9ppb (4.9 µg/l) or ***>4.9ppb (4.9 µg/l)***
4	MA	Do et al. (2005)	Canada 1994-1997	486 pancreatic ca incidence cases matched with 3,596 controls from Canadian population 1995 approximately 29 million	29	Pancreatic [Incident]	N	4 levels, **TTHM**, <10 µg/l, ***10-20µg/l, 20-50µg/l, >50µg/l (ppb)*** **Chloroform (Trichloromethane,TCM)** <3µg/l, 3-10µg/l, 10-30 µg/l, ***>30µg/l*** **Bromodichloromethane (BDCM)** 1-3 µg/l, 3-5 µg/l, ***>5 µg/l***
5	MA	Fagliano (1998)	USA (New Jersey) 1979-1991	166 diagnosed brain ca, 906 controls from 7.5 million people (1983 New Jersey census)	7.5	Childhood Brain [Incident]	N	**TTHM** 4 levels <10 µg/l, ***10-49 µg/l, >=50µg/l, >=66µg/l (ppb)***

Table 2 continued

Included /Excluded in MA (Meta-Analysis)		Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
6	MA	Gottlieb et al. (1982)	USA Louisiana 1960-1975	10,205 Cancer deaths matched controls non-cancer deaths from 13 Louisiana parishes approx. 1.2 million people	1.2	Cancers grouped by hypothesized risk [Mortality] High – bladder, colon, kidney, liver, lymphoma, rectum and stomach. Low – Hodgkin's lymphoma, leukaemia, lung, malignant melanoma, multiple myeloma and prostate and Questionable – breast, brain, oesophagus and pancreas.	Y – Rectum, Kidney, Lung and breast.	Surface vs. ground, ***chlorinated vs. non-chlorinated***, life time exposure estimated.
7	MA	Gottlieb & Carr (1982)	USA (Southern Louisiana) 1960-1975	11,349 ca deaths from 13 parishes in Southern Louisiana, approx. 1.5 million people	1.5	18 Cancers [Mortality] - Liver, Brain, Pancreas, Bladder, Kidney, Prostate, Rectum, Colon, Oesophagus, Stomach, Non-Hodgkin's Lymphoma, Multiple Myeloma, Leukaemia, Hodgkin's disease, Lung, Breast, Malignant Melanoma.	Y – Rectum, Brain, Breast and multiple myeloma, higher order interaction for Pancreas, Prostate, Stomach,	**Chlorinated** (2 levels; ***above*** and below the mean value of chlorine at discharge from water treatment plant, ***1090 µg/l***) vs. Non-chlorinated ground water nil, low <=1.09 ppm, (1090) and ***high >1.09 ppm (1090) µg/l, (ppb)***

Table 2 continued

Included /Excluded in MA (Meta-Analysis)		Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
8	MA	Ijsselmuiden et al. (1992)	USA Maryland 1975-1989	101 first time diagnosis pancreatic ca cases, 206 controls from 89,000 people in Washington county, Maryland.	0.09	Pancreatic [Incident]	Y- Pancreas	***Mean Chloroform level107 µg/l (ppb)*** range 50-150 µg/l. water source city or rural Smoking / non smoking 3 levels of smoking 5 Exposure lengths 35-39, ***40-49, 50-59, 60-69, >=70 yrs. of age, smokers excluded***
9	Excluded from MA	Infante-Rivard et al. (2001)	Canada 1980 - 1993 1991 – 1993	491 diagnosed cases 0-9 yrs. old matched controls, Canadian population 1995 approximately 29 million	excluded	Childhood leukaemia [Incident]	N	TTHM Average level (TTHM, baseline:<=95th percentile) >95thpercentile Average level (TTHM, baseline:<=24th percentile) 25th-75th percentile >75th percentile Cumulative Exposure (TTHM, baseline:<=95th percentile) >95thpercentile Average level (TTHM, baseline:<=24th percentile) 25th-75th percentile >75th percentile Value at Cut-off µg/l (ppb) Chloroform 101.1 Bromoform 0.48 Bromodichloromethane 11.2 Chlorodibromomethane 4.1 µg/litre-days Chloroform 173,280 Bromoform 770 Bromodichloromethane 25,900 Chlorodibromomethane 7,783

Table 2 continued

Included /Excluded in MA (Meta-Analysis)		Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
10	MA	Koivusalo et al. (1998)	Finland 1991 – 1992 1950 - 1987	703 kidney ca cases, 914 controls from entire population of Finland approx. 5 million people 1985 census	5	Urinary tract [Incident]	Y – Kidney for men.	Mutagenicity 4 levels, non-exposed, Low (1-999 net rev/l), Med (1,000-2,499 net rev/l), High (>=2,500 net rev/l) and ***3,000 net rev/l*** for time exposures 2 time exposures Any exposure or ***>=30 yrs. of estimable exposure***
11	MA	Kukkula & Lofroth (1997)	Finland 1971 - 1991	183 pancreatic ca cases, 366 controls from entire population of Finland approx. 5 million people 1985 census	5	Pancreatic [Incident]	N	***chlorinated***/non-chlorinated with 6-time exposure 0, 1, 5, ***10, 15, or 20 yrs.***
12	MA	Liao et al. (2012)	Taiwan 1998 – 2007	500 kidney ca deaths, 302 males, 198 females, from 65 of 365 municipalities	?	Kidney [Mortality]	N	TTHM ppb range no specific number <4.9ppb (4.9 µg/l) or ***>4.9ppb (4.9 µg/l)***
13	MA	Nelemans et al. (1994)	Netherlands 1988 - 1990	128 melanoma patients, 168 controls from approx. 1.3 million people.	1.3	Cutaneous melanoma [Incident]	Y – Cutaneous melanoma	Polluted vs non-polluted Swimmers in pools, open water or any open water and by age ***Chlorination*** vs non chlorination, time exposure based on age. ***<15, 15-25***, >25 yrs. of age
14	MA	Tao et al. (1999)	China (Shangai) 1984 - 1988	71 oesophageal ca deaths matched with 1,122 controls all males, 12 million people (1987 census)	12	Oesophageal [Mortality]	Y	mutagenic or not, ***chlorinated*** or not
15	MA	Tsai et al. (2013)	Taiwan 2006-2010	881 oesophageal ca deaths matched controls from 65 of 365 municipalities	?	Oesophageal [Mortality]	N	TTHM ppb range no specific number <4.9ppb (4.9 µg/l) or ***>4.9ppb (4.9 µg/l)***
16	MA	Young (1983)	USA Wisconsin 1972-1977	1830 white female cancer deaths matched control all white female deaths between 1972-1977 (n=16,058)	.02	(10 cancers, [Mortality] Stomach, Colon, Rectum, Liver, Gall Bladder & Bile duct, Pancreas, Urinary Bladder, Kidney, Brain, Lung & Bronchus, Breast	Y – Colon, Stomach, Pancreas, Colon, Liver, Lung	Average daily chlorine dose over past 20 yrs. or not 0, low 0.01-0.99, ***med 1.0-1.7, high 1.71-7.0 mg/l (ppm)*** Average daily chlorine residual 20 yrs past 0, low 0.01-0.50, ***high 0.51-2.0***

Table 2 continued

Included /Excluded in MA (Meta-Analysis)		Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
Remaining Studies in Table 4 are Cohort studies (n=16) with the exception of *Brenniman et al. 1979 which is a Case Control study.								
1	MA	*Brenniman et al. (1979)	USA (Illinois) 1973-1976	3208 Ca deaths matched with 43,666 controls (1:14) 1.1 million people, whites only because black population was small.	1.1	Oesophagus, Stomach, Large intestine, Rectum and rectosigmoid junction, Liver and intrahepatic bile ducts, Gall bladder and bile ducts, Pancreas, Bladder, Other and unspecified urinary organs. [Mortality]	Y – combined oesophageal, pancreas and stomach men oesophageal, pancreas women stomach	***Chlorinated*** or non-chlorinated
2	MA	Doyle et al. (1997)	USA (Iowa) 1986	28,237 Iowa women from approx. 42,000 post-menopausal women between the ages of 55 - 69	.04	11 Cancers [Incident]	Y – Colon and all cancers combined	***chlorinated surface***, mixed, ground water or chloroform 4 levels (ppb), 0, 1-2, 3-13, 14-287 µg/l
3	MA	Koivusalo et al. (1997)	Finland 1970 – 1993 1955 - 1970	621,431, approx. 14% of Finnish population or 32% of study cohort population, (population of Finland approx. 5 million people 1985 census)	5	26 Cancers [Incident]	Y - women bladder, rectum, oesophagus and breast. In women Non-Hodgkin's lymphoma and melanoma almost significant. Men Lung	***Mutagenicity 3000 net rev/l***

Table 2 continued

Included /Excluded in MA (Meta-Analysis)		Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
4	MA	Koivusalo et al. (1994)	Finland 1955 1970	All cancer cases recorded in Finland 1977 – 1986 16,274 cases 1967 - 1976 15,169 cases (population of Finland approx. 5 million people 1985 census)	5	Stomach, Colon, Rectum, Kidney and Bladder [Incident]	Y – Bladder, Kidney and Stomach	***Mutagenicity*** ***3000 net rev/l***
5	MA	Koivusalo et al. (1995)	Finland 1977 - 1989 1966 - 1976 1950 1970	Approx. half the total population of Finland (approx. 2.2 million in 1970, 1.7 million in 1955 and 2.3 million in 1985)	1.1 (50% x 2.2)	Leukaemia, lymphomas, liver, pancreas and soft tissue, acute and chronic lymphatic and myeloid leukaemia, Hodgkin's and non-Hodgkin's [Incident]	Y – Lymphomas and Pancreatic ca	***Mutagenicity*** ***3000 net rev/l***
6	MA	Wilkins & Comstock (1981)	USA Maryland 1963 - 1975	Approx. 31,000 from Washington County, approx. 100,000 people.	0.1	Biliary passages, Liver, Kidney, Bladder [Incident]	Y - Bladder in men and Liver in women.	***Municipal chlorinated water mean chloroform 107 µg/l (107 ppb)***
Studies reporting Correlation Coefficients n=4								
1	Excluded from MA	Cantor et al. (1978)	USA (Nation) 1968 - 1971	Whites only with 1960 population as the standard. 923 counties over 50% urban in 1970. Approx. 181 million people 1960 census.	excluded	Stomach, Pancreas, Lung, Bladder, Kidney, Brain, Non-Hodgkin's lymphoma [Mortality]	Y – Bladder and Brain in both men and women and Non-Hodgkin's lymphoma and kidney ca in males.	Chloroform, bromine-containing THM (BTHM) and TTHM used as indicator of chlorination and correlated to percent of population served by THM indicator as low (50-64%), intermediate (65-84%) or High (85-100%) and additional grouping of 50-100%

Table 2 continued

Included /Excluded in MA (Meta-Analysis)	Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
2 Excluded from MA	Flaten (1992)	Norway 1980	170,695 people from chlorinating communities pair matched with 106,346 in non-chlorinating communities in 1970	excluded	15 Cancers [Incident]	Y – Colon and Rectum for both men and women.	3 levels of chlorination 1. At least 60% of the population have received chlorinated water at least from 1965 (57 chlorinating municipalities) 2. No waterworks has ever delivered chlorinated water (21 non chlorinating municipalities) 3. Less than 60% of the population received chlorinated water, or chlorination was started later than 1965 at one or more of the waterworks (18 partly chlorinating municipalities) Only 4 of the 183 major waterworks in the 96 municipalities use ground water (non-chlorinating) supplying a total of 4000 people. The other179 waterworks use lakes or rivers.
3 Excluded from MA	Foster et al. (1997)	South West England 1984 - 1988	1.4 million	excluded	Leukaemia [Incident]	Y – Acute leukaemia's and Myeloproliferative disorders.	THM range 0-246 µg/l (ppb)
4 Excluded from MA	Kool et al. (1981)	Netherlands 1965 -1976	Approx. 1/3 of Dutch population, 4.6 million people in 20 communities	excluded	Oesophagus, Stomach, Colon, Rectum, Liver, Bladder, Lung [Mortality]	Y – Higher Cancer mortality rate for Liver, Bladder and Lung Ca.	Surface or ground Chlorinated or not
Studies reporting Regression Analyses n=3							
1 Excluded from MA	Carlo & Mettlin (1980)	USA (Erie County, New York) 1973 - 1976	4,255 cancer cases from approx. 1 million people	excluded	Oesophageal, Stomach, Colon, Rectal, Bladder, and Pancreatic [Incidence]	Y – white males pancreatic ca.	Surface vs Ground THM

Table 2 continued

Included /Excluded in MA (Meta-Analysis)		Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
2	Excluded from MA	Clark et al. (1986)	USA (Nation) 1957 - 1972	National USA	excluded	GI, UT, Oesophagus, Stomach, Large Intestine, Rectum, Liver, Pancreas, Lung, Breast, Kidney, Bladder & all cancers combined [Mortality]	Y – GI and UT cancers	Carbon alcohol extract (CAE) and Carbon chloroform extract (CCE)
3	Excluded from MA	Wigle et al. (1986)	Canada (Nation) 1973 - 1979	National survey of 66 Canadian cities, Canadian population 1995 approximately 29 million	excluded	12 Cancers [Mortality]	Y – Bivariate analysis Stomach Ca, Multiple regression confirmed the association between TOC (total organic carbon) and Large intestine in men.	Total organic carbon (TOC) mg/l, THM µg/l, THM excluding chloroform µg/l, Chlorine dose ppm,
Studies reporting as Mortality Rates n=2								
1	MA	Vinceti et al. (2004)	Northern Italy 1965 - 1987	5,144 residents of Guastalia, Nth Italy from total population of approx. 433,000	0.43	15 Cancers + all cancers combined [Mortality]	Y – Melanoma, stomach, liver, lung, prostate and bladder	***High THM content >40µg/l (40 ppb) 70.7 µg/l (71ppb)*** Chloroform >33 µg/l
2	MA	Yang et al. (1998)	Taiwan (Nation) 1982 - 1992	from 65 of 365 municipalities	?	11 Cancers + all cancers combined [Mortality]	Y – Rectum, Lung, Bladder and Kidney	***Chlorinated (90% of the population is served chlorinated water)*** vs non chlorinated (<5% of the population is served chlorinated water)

Table 2 continued

Included /Excluded in MA (Meta-Analysis)	Author/ Year	Location/ Study Duration	Population	Total pop. (10^6)	Cancers Studied and outcome.	Significant Results Y=yes N=No	Exposure metric ***Exposures used in meta-analysis***
Studies reporting as Rate Ratio n=1							
1 MA	Marcus et al. (1998)	USA (North Carolina)	5,416 whites & 1,046 blacks from total female population ages 35-84 of 960,335 (44% of North Carolina population	1	Breast [Incidence]	Equivocal, weak to no association	4 levels THM (ppb) <40, ***40-<60, 60-<80, >80 ppb***
Studies reporting as Incident Rates n=1							
1 Excluded from MA	Bean et al. (1982)	USA (Iowa)	approx. 1.9 million, over 98% whites, 1.2% black and 0.3% other race.	excluded	[Incidence]	Y bladder, lung & rectum	Surface vs ground
TOTAL population estimate represented by 24 studies **Included in CMA** (without Taiwanese studies)				**80 mil**			

Table 3 Summary statistics for all meta-analyses

Analysis	Number of included studies	risk index	95% Confidence interval Lower	95% Confidence interval Upper	p-value	Predictive interval Lower	Predictive interval Upper	Heterogeneity measures (Q, [df], p, I^2, Tau^2)
Meta-analysis								
all cancer	24	1.125	1.065	1.190	0.000	0.889	1.424	487.4 [23] <0.01, 95.3, 0.012
all cancer cohort	8	1.146	1.064	1.230	0.000	0.912	1.439	118.22 [7] <0.01, 94.1, 0.092
all cancer case control	16	1.100	1.027	1.178	0.007	0.884	1.369	119.7 [15] <0.01, 87.5, 0.009
Geographical location								
North America: all cancers	12	1.090	1.024	1.161	0.007	0.898	1.324	84.2 [11] <0.01, 86.9, 0.006
Europe: all cancers	7	1.153	1.049	1.267	0.003	0.851	1.563	144.9 [6] <0.01, 95.9, 0.012
Asia: all cancers	5	1.119	0.954	1.312	0.167	0.663	1.889	13.8 [4] <0.01, 71.1, 0.020
Gender								
Male: all cancers	11	1.102	1.029	1.179	0.005	0.895	1.356	79.5 [12] <0.01, 87.4, 0.007
Female: all cancers	14	1.062	1.011	1.117	0.017	0.922	1.224	39.96 [13] <0.01, 67.5, 0.004

Table 3 continued

Analysis	Number of included studies	risk index	95% Confidence interval Lower	95% Confidence interval Upper	p-value	Predictive interval Lower	Predictive interval Upper	Heterogeneity measures (Q, [df], p, I^2, Tau^2)
Cancer site								
Statistically significant cancer sites								
Breast	8	1.223	1.086	1.377	0.001	0.874	1.710	19.3 [7] <0.01, 63.7, 0.015
Female reproductive	4	1.167	1.029	1.324	0.016	0.885	1.540	1.9 [3] 0.60 0.00, 0.000
non-Hodgkin's	5	1.309	1.231	1.393	0.000	1.169	1.467	4.1 [4] 0.39, 2.24, 0.000
Melanomas	5	1.438	1.027	2.013	0.034	0.454	4.554	21.0 [4] <0.01, 81.2, 0.102
Lung	6	1.165	1.092	1.243	0.000	1.063	1.277	3.6 [5] 0.61, 0.00, 0.000
Non-significant cancer sites								
Brain and nervous	8	0.979	0.722	1.326	0.889	0.378	2.536	44.2 [7] <0.01, 84.2, 0.128
Prostrate	4	1.010	0.885	1.153	0.880	0.756	1.350	2.2 [3] 0.54, 0.00, 0.000
Upper digestive tract	10	1.062	0.992	1.136	0.082	0.902	1.250	32.5 [9] <0.01, 72.2, 0.000
Oesophageal	6	1.135	0.933	1.381	0.205	0.650	1.982	16.2 [5] <0.01, 69.0, 0.030
Stomach	7	1.045	0.978	1.117	0.193	0.887	1.231	17.2 [6] <0.01, 65.2, 0.030
Liver and Gall bladder	7	1.193	0.932	1.527	0.162	0.551	2.584	86.0 [6] <0.01, 93.0, 0.075
Liver	7	1.219	0.942	1.576	0.132	0.544	2.730	81,2 [6] <0.01, 92.6, 0.081
Gallbladder & ducts	2	1.038	0.884	1.218	0.652	na	na	na

Table 3 continued

Analysis	Number of included studies	risk index	95% Confidence interval Lower	95% Confidence interval Upper	p-value	Predictive interval Lower	Predictive interval Upper	Heterogeneity measures (Q, [df], p, I^2, Tau^2)
Pancreas	11	1.056	0.945	1.180	0.340	0.752	1.482	117.3 [10] <0.01, 91.5, 0.019
Urinary tract (excluding bladder)	10	0.996	0.782	1.268	0.974	0.436	2.274	145.3 [9] <0.01, 93.8, 0.113
Kidney	9	0.996	0.744	1.335	0.980	0.372	2.668	116.1 [8] <0.01, 93.1, 0.152
Immune cancers combined	6	1.088	0.953	1.242	0.211	0.753	1.572	16.71 [5] ,0.01, 70.1, 0.013
Hodgkin's	3	1.108	0.948	1.295	0.198	na	na	3.0 [2] 0.23, 32.8, 0.007
Leukaemia	5	1.016	0.889	1.161	0.814	0.693	1.489	8.0 [4] 0.09, 49.7, 0.010
Soft tissue	2	1.073	0.965	1.193	0.194	na	na	na
Single studies								
Cervical	1	1.710	0.498	5.871	0.394	na	na	na
Corpus luteum	1	1.090	0.883	1.345	0.422	na	na	na
Endometrium	1	1.434	0.991	2.077	0.056	na	na	na
Skin cancer excluding basal cell carcinoma	1	1.099	0.937	1.290	0.246	na	na	na
Testis	1	1.120	0.772	1.625	0.550	na	na	na
Thyroid	1	0.953	0.807	1.125	0.568	na	na	

Table 4 Estimate of absolute reduction in cancer incidence and mortality statistically significant results

Result	Relative Effect (CI 95%)	Cancer Incident Estimated Absolute Reduction Per 100,000 population (Range)	Cancer Mortality Estimated Absolute Reduction Per 100,000 population (Range)
All reported cancers, all geographical regions, both genders.	13% (7% - 19%)	24 (13 – 35)	13 (7 – 19)
North America: all cancers	9% (2% - 16%)	16 (4 – 29)	9 (2 – 16)
Europe: all cancers	15% (5% - 27%)	27 (9 – 49)	15 (5 – 28)
*Asia: all cancers	12% (10% - 31%)	22 (18 – 56)	12 (10 – 32)
Male: all cancers	10% (3% - 18%)	18 (6 – 33)	10 (3 -18)
Female: all cancers	6% (1% - 12%)	11 (2 – 22)	6 (1 – 12)
Breast	22% (9% - 38%)	40 (16 – 69)	22 (9 – 39)
Female Reproductive	17% (3% - 32%)	31 (6 – 58)	17 (3 – 33)
Melanomas	44% (3% - 113%)	80 (6 – 206)	44 (3 - 115)
Non-Hodgkin's	31% (23% - 39%)	56 (42 – 71)	31 (23 – 40)
Lung	17% (9% - 24%)	31 (16 - 44)	31 (9 – 25)

*Asia: all cancers although not a significant result is included for completeness.

Supplemental Material

Appendix 1 Data Bases Searched, Logic Grid and PubMed Search String*.

Database			
Peer Reviewed	PubMed, Embase, Scopus, Cochrane Library, Web of Science		
Government	USEPA, US Dept. Health and Human Services, USDA, Health Canada, European Union, Australian NHMRC		
Water Industry	American Water Works Association, Association of State Drinking Water Administrators, Association of Metropolitan Water Agencies, National Rural Water Association, National Association of Water Companies, Water Research Foundation		
Grey Literature	Proquest Dissertations & Theses Database, Mednar Grey, WHO, Trove, Conference Proceedings		
\PICO)			
P (population)	I (intervention)	C (comparator)	O (outcome)
(human[tw] OR humans[tw] OR persons[mh] OR men[tw] OR women*[tw] OR woman*[tw] OR age groups[mh] OR child*[tw] OR adolescen*[tw] OR teen*[tw] OR youth*[tw] OR minor[tw] OR homo[tw])	(disinfection by product*[tw] OR disinfection byproduct*[tw] OR chlorinat*[tw] OR chlorine[tw] OR chlorine/chemistry[mh] OR purification by product*[tw])	(water supply[mh] OR water suppl*[tw] OR water purification*[tw] OR drinking water[tw] OR potable[tw] OR treated water*[tw] OR swim*[tw] OR bath*[tw] OR shower*[tw])	(neoplasms[mh] OR neoplas*[tw] OR tumoregen*[tw] OR tumor[tw] OR tumors[tw] OR tumori*[tw] OR tumoro*[tw] OR tumour*[tw] OR cancer*[tw] OR carcino*[tw] OR peroxisome proliferator*[tw] OR oncogen*[tw] OR aneugen*[tw] OR mutagen*[tw] OR sarcom*[tw] OR adenocarcin*[tw] OR adenoma*[tw] OR argentaffinoma*[tw] OR Cholangiocarcinoma[tw] OR Choriocarcinoma[tw] OR Malignan*[tw] OR Cylindroma[tw] OR Cystadenocarcinoma[tw] OR dermoid*[tw] OR Teratoma*[tw] OR Fibroadenoma[tw] OR Adenofibroma[tw] OR Fibrosarcoma[tw] OR Gastrinoma[tw] OR Glucagonoma[tw] OR Leiomyosarcoma[tw] OR leukemia*[tw] OR leukoplakia[tw] OR melanoma[tw] OR neuroblastoma[tw] OR odontoma[tw] OR Paget's Disease, Mammary[tw] OR Paget Disease, Extramammary[tw] OR Rhabdomyosarcoma[tw] OR Somatostatinoma[tw] OR struma ovarii[tw] OR vipoma[tw] OR neoplasms[mh] OR neoplasm*[tw] OR cancer*[tw] OR malignan*[tw] epidemiolog*[tw] OR

09 November 2012 PubMed Search String	(neoplasms[mh] OR neoplas*[tw] OR cancer*[tw] OR malignan*[tw]) AND (chlorinated water[tw] OR (water supply[mh] OR water suppl*[tw] OR water purification[tw] OR drinking water[tw] OR potable[tw] OR treated water*[tw] OR water treatment*[tw] OR swim*[tw] OR bath*[tw] OR shower*[tw]) AND (disinfection by product*[tw] OR disinfection byproduct*[tw] OR purification by product*[tw] OR trihalomethanes[mh] OR trihalomethane*[tw] OR bromodichloromethane[tw] OR bromoform[tw] OR chlorodibromomethane[tw] OR chloroform[tw] OR dibromochloromethane[tw] OR dichlorobromomethane[tw] OR tribromomethane[tw] OR trichloromethane[tw] OR trihalomethane*[tw] OR total organic halide*[tw] OR chlorine/chemistry[mh] OR chlorinat*[tw] OR chlorine[tw] OR disinfection by product*[tw] OR disinfection byproduct*[tw] OR purification by product*[tw] OR purification byproduct* OR halogenation[tw] OR chloroacet*[tw] OR monochloroacet*[tw] OR chloro acetate[tw] OR bromoacet*[tw] OR monobromoacet*[tw] OR dichloroacet*[tw] OR bichloroacetic acid[tw] OR dibromoacet*[tw] OR trichloroacet*[tw] OR bromate*[tw] OR chlorite[tw] OR halonitromethane*[tw] OR chloronitromethane[tw] OR bromonitromethane[tw] OR dichloronitromethane[tw] OR dibromonitromethane[tw] OR bromochloronitromethane[tw] OR trichloronitromethane OR chloropicrin*[tw] OR bromodichloronitromethane[tw] OR dibromochloronitromethane[tw] OR tribromonitromethane[tw] OR iodoacetic acid[mh] OR iodoac*[tw] OR iodacet*[tw] OR moniodoacet*[tw] OR monoiodac*[tw] OR monoiodine acetate[tw] OR bromoiodoacet*[tw] OR bromochloroacet*[tw] OR dibromochloroacet*[tw] OR tribromoacet*[tw] OR dichloroiodomethane[tw] OR bromochloroiodomethane[tw] OR dibromoiodomethane[tw] OR chlorodiiodomethane[tw] OR bromodiiodomethane[tw] OR iodoform[tw] OR tri iodomethane[tw] OR triiodomethane[tw] OR dichloromethane[tw] OR bromochloromethane[tw] OR chlorobromomethane[tw] OR methylene bromide[tw] OR dibromomethane[tw] OR mucochloric acid[tw] OR haloamide*[tw] OR chloroacetamide[tw] OR chloracetamide[tw] OR haloacetonitrile*[tw] OR tribromopyrrole[tw] OR nitrosamines[mh] OR ndma[tw] OR n nitrosopyrrolidine[tw] OR n nitrosomorpholine[tw] OR n nitrosopiperidine[tw] OR n nitrosodiphenylamine[tw] OR formol[tw] OR methanal[tw] OR acetaldehyde[tw] OR ethanal[tw] OR chlorate*[tw])) AND (human[tw] OR humans[tw] OR persons[mh] OR men[tw] OR women[tw] OR woman*[tw] OR age groups[mh] OR child[mh] OR child*[tw] OR adolescen*[tw] OR teen* OR youth*[tw] OR minors[tw] OR homo[tw]) NOT (animals[mh] NOT humans[mh]) NOT (food contamination[mh] OR food microbiology[tw]) AND (epidemiologic studies[mh] OR epidemiologic stud*[tw] OR epidemiological stud*[tw] OR case-control studies[mh] OR case control*[tw] OR case base*[tw] OR case referent*[tw] OR case compeer*[tw] OR case comparison*[tw] OR cohort studies[mh] OR cohort stud*[tw] OR concurrent stud*[tw] OR incidence stud*[tw] OR cohort analys*[tw] OR longitudinal stud*[tw] OR longitudinal survey*[tw] OR longitudinal evaluation[tw] OR longitudinal method[tw] OR follow up stud*[tw] OR followup stud*[tw] OR prospective stud*[tw] OR prospective analys*[tw] OR retrospective stud*[tw] OR retrospective design[tw] OR retrospective panel stud*[tw] OR cross sectional stud*[tw] OR cross sectional analys*[tw] OR cross sectional method[tw] OR cross sectional survey*[tw] OR cross sectional design*[tw] OR cross sectional research[tw] OR disease frequency survey*[tw] OR prevalence stud*[tw] OR seroepidemiologic stud*[tw] OR seroepidemiological stud*[tw] OR seroprevalence*[tw] OR epidemiolog*[tw])		

*Automated search updates have yielded no new studies meeting search criteria to date.
Limiter to Human Studies: NOT (animals[mh] NOT humans[mh])

Modified Study filter, refer to Adelaide University Library URL for original[a]

NOT (food contamination[mh] OR food microbiology[tw]) AND (epidemiologic studies[mh] OR epidemiologic stud*[tw] OR epidemiological stud*[tw] OR case-control studies[mh] OR case control*[tw] OR case base*[tw] OR case referent*[tw] OR case compeer*[tw] OR case comparison*[tw] OR cohort studies[mh] OR cohort stud*[tw] OR concurrent stud*[tw] OR incidence stud*[tw] OR cohort analys*[tw] OR longitudinal stud*[tw] OR longitudinal survey*[tw] OR longitudinal evaluation[tw] OR longitudinal method[tw] OR follow up stud*[tw] OR followup stud*[tw] OR prospective stud*[tw] OR prospective analys*[tw] OR retrospective stud*[tw] OR retrospective design[tw] OR retrospective panel stud*[tw] OR cross sectional stud*[tw] OR cross sectional analys*[tw] OR cross sectional method[tw] OR cross sectional survey*[tw] OR cross sectional design*[tw] OR cross sectional research[tw] OR disease frequency survey*[tw] OR prevalence stud*[tw] OR seroepidemiologic stud*[tw] OR seroepidemiological stud*[tw] OR seroprevalence*[tw] OR epidemiolog*[tw])

[a]Adelaide University Library URL link for study filters http://www.adelaide.edu.au/library/guide/med/studytypes.html#e2

Appendix 2 JBI CReMS (Comprehensive Review Management System) Quality Assessment

Number	Author Study type	Year	No answers	Unclear answers	Not applicable answers	5 yes answers ACCEPTABLE MET CRITERIA	6-7 yes answers MEDIUM QUALITY	8-9 yes answers HIGH QUALITY
1	Alavanja et. al. Case control	1977		2			7	
2	Bean et. al. Cohort	1982		1				8
3	Brenniman et. al. Case control	1979	1					8
4	Cantor et. al. Cohort	1978			2		7	
5	Cantor et. al. Case control	1999						9
6	Carlo & Metlin Cohort	1980	1	1	1		6	
7	Chiu et. al. Case control	2010						9
8	Clark et. al. Cohort	1986	1	1	1		6	
9	Do et. al. Case control	2005		2			7	
10	Doyle et. al. Cohort	1997		1				8
11	Fagliano Case control	1998	1					8
12	Flaten Cohort	1992	1		1		7	
13	Foster et. al. Cohort	1997	1	1			7	
14	Gottlieb et. al. Case control	1982			1			8
15	Gottlieb & Carr Case control	1982						9
16	Ijsselmuiden et. al. Case control	1992		1				8
17	Infante-Rivard et. al. Case control	2001						9
18	Koivusalo et. al. Case control	1998		1				8
19	Koivusalo et. al. Cohort	1994		1				8
20	Koivusalo et. al. Cohort	1997						9
21	Koivusalo et. al. Cohort	1995			1			9

Number	Author Study type	Year	No answers	Unclear answers	Not applicable answers	5 yes answers ACCEPTABLE MET CRITERIA	6-7 yes answers MEDIUM QUALITY	8-9 yes answers HIGH QUALITY
22	Kool et. al. Cohort	1981	1		3	5		
23	Kukkula & Lofroth Case control	1997	1	2			6	
24	Liao et. al. Case control	2012		1				8
25	Marcus et. al. Cohort	1998	1		3	5		
26	Nelemans et. al. Case control	1994	1					8
27	Tao et. al. Case control	1999	1					8
28	Tsai et. al. Case control	2013	1					8
29	Vincenti et. al. Cohort	2004						9
30	Wigle et. al. Cohort	1986			3		6	
31	Wilkins et. al. Cohort	1981	1	1			7	
32	Yang et. al. Cohort	1998			1			8
33	Young Case control	1983			1			8
T0TALS			**7**	**7**	**13**	**2 (6%)**	**9 (27%)**	**22 (67%)**

Critical appraisal criteria for comparable cohort / case control studies:
(JBI Meta-Analysis of Statistical Assessment and Review Instrument (MAStARI), The Joanna Briggs Institute, 2014)
1) Is sample representative of patients in the population as a whole? 2) Are the patients at a similar point in the course of their condition / illness? 3) Has bias been minimalized in relation to selection of cases and of controls? 4) Are confounding factors identified and strategies to deal with them stated? 5) Are outcomes assessed using objective criteria? 6) Was follow up carried out over a sufficient time period? 7) Were the outcomes of people who withdrew described and included in the analysis? 8) Were outcomes measured in a reliable way? 9) Was appropriate statistical analysis used?

Appendix 3 Confounders

Number of Confounders Reported	Paper	Total papers
15	Flaten 1992	1
14	Do et. al. 2005, Ijsselmuiden et. al. 1992,	2
13	Chiu et. al. 2010, Liao et. al. 2012, Tsai et. al. 2013,	3
12	Doyle et. al. 1997	1
11	Fagliano 1998	1
10	Koivusalo et. al. 1998,	1
9	Tao et. al. 1999, Wilkins & Comstock 1981, Wigle et. al. 1986	3
8	Cantor et. al. 1999, Nelemans et. al. 1994, Cantor et. al. 1978, Kool et. al. 1981, Marcus et. al. 1998, Bean et. al. 1982	6
7	Koivusalo et. al. 1994, Koivusalo et. al. 1995, Carlo & Metlin 1980	3
6	Gottlieb et. al. 1982, Infante-Rivard et. al. 2001, Koivusalo et. al. 1997, Foster et. al. 1997	4
5	Vincenti et. al. 2004	1
4	Alavanja et. al. 1977, Gottlieb & Carr 1982	2
3	Young 1983, Brenniman et. al. 1979, Yang et. al. 1998	3
2	nil	nil
1	Clark & Goodrich 1986	1
None	Kukkula & Lofroth 1997	1

List of confounders as reported by study authors.

Reporting by ODDS RATIO (n=16)

1. **Alavanja et. al. 1977**

   Independent variables (total 4):

   1. Place of residence; urban or rural.
   2. Residence in an area served by chlorinated or non-chlorinated water.
   3. Residence in an area served by surface or ground water.
   4. Occupation; classified as either low or high cancer risk.
      High cancer risk occupations;
      steel, metal processing, mining, printing, chemical, furniture manufacturing, automobile fabrication, rubber and electrical cable manufacturing.

   Cases were matched for age (to nearest year), race, sex, foreign vs. US born and county of usual residence.

2. **Cantor et. al. 1999**

   Confounders (total 8)

   Odds ratios were adjusted for several known or suspected risk factors using unconditional logistic regression analysis with case-control status as the response variable. Where appropriate the following potential confounding variables in regression models (in addition to the drinking water exposure of interest):
   1. sex
   2. age, years (four strata)
      a. 40-54
      b. 55-64
      c. 65-74
      d. 75-85

3. ever employed as a farmer
4. population size of places of residence (based on 1980 census) averaged over lifetime.

Tests of linear trend and of homogeneity of trend were based on standard score statistics [20]. The trend tests used the exposure metric of interest as a continuous variable. Several other factors were evaluated in logistic models and ruled out as potential confounders:

1. brain cancer in a first-degree relative
2. employment (ever) in a high risk (non-agricultural) occupation for brain cancer in this study
3. dietary variables describing the consumption frequency of several individual foods and food groups
4. intake level of tap water and total beverages

3. **Chiu et. al. 2010**

(total 13 confounders accounted for 9 consolidated into 1 then further subdivided into 4 see below)

1. Socioeconomic factors accounted for by use of an "urbanisation index". Because mortality from cancer is associated with urbanisation gradients (Tzeng and Wu, 1986). The urbanisation index used serves as a proxy for a large number of explanatory variables, such as population density, age composition, mobility, economic activity and family income, educational level, environmental factors and health service related facilities. For analyses the urban – rural classification was further subdivided into four levels.
    1. metropolitan
    2. city
    3. town
    4. rural

4. **Do et. al. 2005**

Confounders (total 14, 11 + 3 additional for females)

Unconditional logistic regression analysis used to explore the effect of CDBP exposure on pancreatic cancer risk. All models adjusted for the three matching variables (age group, sex and province of residence) and for;

1. age group
2. sex
3. province of residence
4. body mass index (BMI)
5. percent weight change
6. smoking
7. coffee,
8. beer
9. liquor
10. total fat intake
11. energy intake

Analysis restricted to females as adjusted for;

1. age at first menstruation
2. number of pregnancies

All continuous confounders were categorised into quartiles before analysis based on their distribution in the combined group of cases and controls. Effect modification by sex was explored by fitting separate logistic regression models for males and for females.

5. **Fagliano 1998**

Covariates (page 67) (total 11)

1. child's sex

2. race
3. birth weight
4. mother and father's race
5. age
6. educational level
7. number of prenatal visits
8. month that prenatal care began
9. gestational age (computed from recorded date of last menses and birth date)
10. number of previous pregnancies (computed from parity and the number of previous terminations)
11. quality of prenatal care (determined from gestational age, month prenatal care began and number of prenatal care visits)

Odds ratios (ORs) and 95% confidence intervals (CI) were computed for drinking water contaminant exposures and for other potential risk factors by stratified analysis and logistic regression using Egret software (38). Analyses were conducted for all cases and by case subgroupings. Confounding and effect modification of the drinking water exposure factors were assessed by computing ORs for each stratum and the Mantel-Haenszel summary ORs (39) across strata of other variables that were associated with brain cancer risk or were associated with the exposure variables. A factor was considered to be a potential confounder if, in the absence of apparent effect modification, the Mantel-Haenszel summary OR differed from the unadjusted OR by more than 15 percent (40) and the unadjusted OR was greater than 1.5 or less than 0.7.

6. **Gottlieb et. al. 1982**

Controls were selected from non-cancer deaths following the removal of out-of-state deaths and confounding causes of death.
Confounding causes were those, aetiologically related to the cancer under investigation such as ulcerative colitis for colon cancer and chronic obstructive respiratory disease for lung cancer.

Confounders (total 6)

1. Industry of occupation (from death certificate)
2. Address, which was then recorded in latitude and longitude and mapped to within 0.32 km)
3. Birthplace
4. Parents names
5. Acadian ancestry (coded according to last name of the parents and the parish of birth, Acadian last names were compiled from those names included on the ships' logs of the original settlers in Louisiana)
6. Length of residence based on water company records, voters registration and city directories. Where this could not be determined (approx. half of the population in question) an alternate method of estimating length of time of water source was developed using place of birth and death categorised as;
    1. mostly surface
    2. some surface
    3. possible surface
    4. least surface

Although the water source in use between birth and death is unknown, this variable reflects a gradient of surface water use such that the mostly surface category contains most of the long-term surface water users, while the least surface category contains fewest of these.

7. **Gottlieb & Carr 1982**

Confounders (total 4)

1. sex
2. race
3. age
4. year of death

A multidimensional contingency table analysis was performed based on log-linear model and utilised maximum likelihood estimations of all main effects and interactions. All of the matching variables were used as possible effect modifiers in the analysis, with age dichotomised at the mean for the site and year of death, dividing the study period in halves. Chlorine was trichotomised into none, low or high and its relationship with disease, or case/control, was examined by sex, race, age and year of death.

8. **Ijsselmuiden et. al. 1992**

Confounders (total 14)

1. age
2. sex
3. race
4. years of schooling
5. employment status
6. history of smoking
7. location of residence
8. marital status
9. years of residence in the present house
10. degree of disability
11. previous cancer history
12. source of drinking water
13. use of water softeners
14. other home water treatment

Odds ratios and their 95% CI were calculated both before and after adjustment by multiple logistic regression using the GLIM statistical package.

9. **Infante-Rivard et. al. 2001**

Confounders (total 6)

1. Mothers level of schooling
   a. college or university
   b. secondary school
   c. none, primary
2. Family income at diagnosis
   d. ≥40,000
   e. 10,000-39,000
   f. <10,000
3. Maternal age (years) at birth of index child
   a. ≤35
   b. >35
4. Paternal age (years) at birth of index child
   a. ≤40
   b. >40
5. Race of mother
   a. white
   b. black
   c. other
6. Maternal smoking first trimester of pregnancy
   a. none
   b. 1-20 cigarettes
   c. >20 cigarettes daily

Conditional logistic regression used to estimate ORs at 95% CI.

10. **Koivusalo et. al. 1998**

Confounders (total 10)

1. Residential history (urbanisation)

2. Smoking (four categories)
    a. non smoker
    b. past smoker
    c. present smoker of 1-19 cigarettes/day
    d. present smoker of ≥ 20 cigarettes/day
3. Lifetime occupational career (used to determine social class)
4. Occupational exposures
    a. chemical
    b. leather
    c. dyeing,
    d. printing
    e. graphic industries
5. Current and previous intake of water
6. Intake of coffee and other beverages including tea
7. Medication during the previous 10 years
8. Weight
9. Height
10. Past urinary tract illnesses (infections and urolithiasis)

Statistical analysis for both cancer sites was conducted by gender using logistic regression models.

11. **Kukkula and Lofroth 1997**

No confounders

12. **Liao et. al. 2012** (same as for **Chiu et. al. 2010)**

1. Socioeconomic factors accounted for by use of an "urbanisation index". Because mortality from cancer is associated with urbanisation gradients (Tzeng and Wu, 1986). The urbanisation index used serves as a proxy for a large number of explanatory variables, such as population density, age composition, mobility, economic activity and family income, educational level, environmental factors and health service related facilities. For analyses the urban – rural classification was further subdivided into four levels.
    1. metropolitan
    2. city
    3. town
    4. rural

13. **Nelemans et. al. 1994**

Confounders (total 8)
1. demographic variables
2. tendency to burn
3. ability to tan
4. indices for sunlight exposure
    a. number of sunburns
    b. number of holidays in sunny countries
    c. average weekly number of hours of sunbathing during the summer months
5. Physical assessment by physician with training in dermatology of
    a. skin
    b. hair
    c. eye colour
    d. degree of freckling
    e. number of naevi on the back
6. age
7. gender
8. educational level as index of socioeconomic status

Correction for differences between cases and controls with respect to potential confounders was allowed for in the analysis by use of multiple logistic regression analyses. The number of naevi was

not seen as a confounder, but as a possible intermediate factor, and was therefore not included in the models.

14. **Tao et. al. 1999**

Confounders (total 9)

1. To control for the effects of urbanisation-related factors such as chlorinated tap water, air pollution and population density the community selection was stratified by urban or rural locations.
2. age
3. medical history
    a. hepatitis
    b. cirrhosis
    c. schistosomiasis
    d. digestive tract ulcer
4. occupational history (with emphasis on selected hazardous occupations) Because of the small number in each occupational subset, a combined indicator, ever exposed to any of the below hazardous occupations was used in the analysis.
    a. alpha, beta, gamma or X-ray
    b. arsenic and its compounds
    c. asbestos
    d. ethylene chloride
    e. chromium and its compounds
    f. cadmium and its compounds
    g. chloromethyl ether
    h. formaldehyde
    i. nickel and its compounds
    j. coal tar
    k. asphalt
    l. acrylonitrile
5. pesticide exposure
6. lifestyle factors
    a. cigarette smoking
    b. tea intake
    c. alcohol intake
7. Dietary intake
    a. pickled vegetables
    b. maize
    c. peanuts
    d. cured meats
8. education
9. monthly food expenses

An unconditional logistic regression was used to estimate the OR and CI for drinking mutagenic water against male oesophageal cancer controlling for possible confounders as listed above. Likelihood ratio tests and a backward method were used to finalise the regression model.

15. **Tsai et. al. 2013** (same as for **Chiu et. al. 2010 and Liao et. al. 2012)**

1. Socioeconomic factors accounted for by use of an “urbanisation index”. Because mortality from cancer is associated with urbanisation gradients (Tzeng and Wu, 1986). The urbanisation index used serves as a proxy for a large number of explanatory variables, such as population density, age composition, mobility, economic activity and family income, educational level, environmental factors and health service related facilities. For analyses the urban – rural classification was further subdivided into four levels.
    1. metropolitan
    2. city
    3. town
    4. rural

16. **Young 1983**

Confounders (total 3)
The confound of perhaps greatest importance is that urban residence is associated with higher cancer mortality (84) and with exposure to chlorinated water.

1. urban residence (ranked on 1960 US census population)
   a. most urban >50,000
   b. 20,001-50,000
   c. 10,001-20,000
   d. 5,001-10,000
   e. 2,501-5000
   f. <2,500
2. Site specific high risk occupations vs. homemaker
   a. Bladder-dyers, shoe makers, hairdressers, painters, printing, print apprentice, textiles
   b. Kidney-dyers
   c. Pancreas-metal production
   d. Liver, biliary-chemicals
   e. Lung, gastrointestinal-asbestos
3. Marital status

RELATIVE RISK (n=6)

17. **Brenniman et. al. 1979**

Total confounders 3

Only chlorinated or non-chlorinated groundwater was used to avoid confounding by comparing chlorinated surface water with non-chlorinated ground water. Control variables included age, sex and residence.

1. Age; collapsed into 6 intervals, two broad age categories (under 25 and 25-44) for those under 45 because in 1979 cancers of the digestive and urinary tract are relatively infrequent. Ten year intervals 45-54, 55-64, 65-75 and >75.
2. Residency; urban/rural and standard metropolitan statistical area (SMSA)/non-standard metropolitan statistical area (non-SMSA). Criteria for SMSA are useful in distinguishing rural-nonfarm populations in non-SMSA counties from SMSA-rural populations that may have urban characteristics.
3. gender

18. **Doyle et. al. 1997**

Information on potential confounding variables was derived from the Iowa Women's Health Study baseline questionnaire.

Confounders (total 12) – all relative risks were adjusted for the following common risk or protective factors shared by most major cancers;

1. Age (years)
   a. 55-59
   b. 60-64
   c. 65-69
2. Residence
   a. Farm
   b. Rural, nonfarm
   c. Town <1000 residents
   d. 1000-2499 residents
   e. 2,500-10,000 residents
   f. >10,000 residents
3. education

a. <high school
b. high school
c. >high school

4. smoking status
   a. never smoked
   b. ex-smoker
   c. current smoker
5. cigarette pack-years
   a. 1-19 pack years
   b. 20-39 pack years
   c. ≥40 pack years
6. leisure time physical activity
   a. low
   b. moderate
   c. vigorous
7. total fruit and vegetable intake (serves/month)
   a. <103
   b. 103-145
   c. 146-197
   d. >198
8. total calorie intake
   a. <1351
   b. 1351-1695
   c. 1695-2103
   d. >2103
9. body mass index
   a. <23
   b. 23-25
   c. 26-29
   d. >29
10. waist to hip ratio
    a. <0.78
    b. 0.78-0.82
    c. 0.83-88
    d. >0.89

Additional adjustments for the following confounders which had previously been found to be risk factors for the corresponding cancer sites in this study population.

11. History of blood transfusion (in analyses of kidney cancer)
    a. no
    b. yes
12. In analyses of cancer of breast, ovary and corpus uteri
    a. age at menarche
    b. age at menopause
    c. age at first pregnancy (quartiles)

19. **Koivusalo et. al. 1997**

Confounders (total 6)

1. Occupation – used to construct the categorical social-status variable
   a. managerial positions
   b. white collar
   c. blue collar
   d. remaining occupations, unemployed and pensionaries
2. Broad age group (years)
   a. 0-49
   b. 50-64
   c. 65-74
   d. >75
3. Time

3. Migration
4. Death
5. Place of residence-degree or urbanisation
6. Water pipe connection

20. **Koivusalo et. al. 1994**

Confounders (total 7)
1. sex
2. age
3. calendar period
4. urban living
5. social class (used to describe)
   a. life style
   b. smoking habits
6. Municipalities with ≥2% of the population working in the chemical industry (excluded)
7. Migration

21. **Koivusalo et. al. 1995**

Confounders (total 7) – A crude analysis was made on the basis of only the exposure to mutagenicity (Wm) in the model in order to observe the change in risk estimates after a step-by-step control of confounding.
1. Age
2. Gender
3. Period
4. Urbanity-i.e. Living in the three main cities of Finland (background factors) were controlled by using categorical variables in the analysis.
5. Social class-used as proxy for
   a. lifestyle
   b. smoking habits
6. Industrial exposure (separate analysis without)
   a. 2% or more of the population working in the chemical industry
   b. 10% or more of the population working in the pulp wood industry
   c. municipalities with more than 10% of the population employed in agriculture
7. Migration
   a. municipalities with average annual migration of more than 8% between 1967 and 1970.

22. **Wilkins & Comstock 1981**

Confounders (total 9)
1. Age
2. Smoking history
3. Marital status
4. Education (years)
5. Church attendance
6. Housing index score
7. Persons per room
8. Years in 1963 domicile
9. Source of drinking water

CORRELATION COEFFICIENTS (n=4)

23. **Cantor et. al. 1978**

Confounders (total 8) – A weighted linear regression model was used to predict sex- and site-specific cancer rates in the 923 US counties over 50% urban in 1970. For each county, the weight was directly proportional to the square root of the county's person-years at risk and hence inversely

proportional to the standard deviation of the estimated mortality rate. The following county level predictor variables were in the regression model:

1. percent urban (1970)
2. median school years completed by person over age 25 (1970)
3. population size (1970)
4. ratio of 1970 to 1950 population
5. percent work force in manufacturing
6. percent foreign stock in each of ten ethnic groups (Asian, Canadian, Eastern European, Finnish, German, Mexican, Northern European, Russian, Scandinavian and Southern European, 1970)
7. County location in one of nine geographical locations

In further analyses, partial correlation coefficients were calculated after controlling for the effect of the percent of the population employed in specific high-risk industries on residual mortality rates. This was done for two sites (bladder and lung) with known or suspected industrial determinants for cancer after a positive association with THM had been observed.

8. High risk industries – Counties with at least 65% of the population served by one water supply.
    a. Bladder - Industries included those with standard industrial codes for rubber, chemical and leather.
    b. Lung - Industries included those with standard industrial codes for paper, chemical, petroleum and transportation.

24. **Flaten 1992**

Confounders (total 15) – apply to 1970 unless otherwise noted.

1. % of population with chlorinated water
2. Fat intake (g/day, 1977-1979)
3. Fibre intake (g/day, 1977-1979)
4. % living in densely populated areas
5. % with telephone
6. Passenger cars per 100 inhabitants
7. Income per resident (1000 NKR)
8. % men with higher education
9. % women with higher education
10. % men in primary industries
11. % women in primary industries
12. % men in secondary industries.
13. % women in secondary industries
14. % men with income from own work
15. % of women with income from own work

25. **Foster et. al. 1997**

Confounders (total 6) – The correlations between the standardised incidence ratios (SIRs) of the individual disease categories plus the two disease groups and the water quality indicators were investigated using both correlation and multiple regression analysis.

1. age
2. date of birth
3. sex
4. date of diagnosis
5. diagnostic code
6. grid reference of the enumeration district of domicile

26. **Kool et. al. 1981**
Confounders (total 8)

1. Raw water source (surface or ground)
2. Treatment process
3. Main organic constituents in nineteen tap waters in 1976
4. Total hardness (used as negative control)
5. Age
6. Sex
7. Cancer mortality rates over twelve years (1965-1976)
8. Population data of the nineteen communities considered

REGRESSION ANALYSIS (n=3)

27. **Carlo & Metlin 1980**
Confounders (Dependent variables) (total 7) – The data were studied by correlations and multiple regressions of the water quality measures and control variables on the age-adjusted incidence rates.

1. age adjusted incidence rates by census tracts for each site for the total population
   a. and for each sex-colour subgroup
2. Mobility -unstable populations e.g. those with large hospitals or universities (nine out of 218)
3. Socioeconomic factors
4. Percent non-white
5. Urbanicity
6. Water source type
7. Total THM

28. **Clark & Goodrich 1986**
Confounders (total 1) – A regression analysis was performed between the sum of carbon alcohol extract (CAE) and carbon chloroform extract (CCE) and cancer mortality.

1. the age adjusted 20-year average cancer mortality rates for those counties with STORage and RETrieval (STORET, USA Environmental protection agency) monitoring locations measuring CAE and CCE served as the dependent variable in the regression analysis.

29. **Wigle et. al. 1986**

Confounders (total 9) – Correlation and multiple regression analysis conducted using the statistical analysis system (SAS).

1. water source
   a. surface
   b. mixed
   c. ground
2. asbestos concentration (millions of fibres/litre in distribution system water samples)
3. fluoridation
   a. no
   b. yes
4. total organic carbon, mg/l (TOC) in distribution water samples
5. trihalomethanes µg/l (ppb)
   a. chloroform
   b. trihalomethanes except chloroform
6. chlorine dose – concentration in ppm (mg/l) in treated water
7. hardness – the concentration of calcium plus magnesium in distribution system water samples expressed as equivalent ppm (mg/l) of $CaCO_3$
8. education - percent <grade nine, (percent of the 1971 population aged 15 or older whose highest education achieved was less than grade 9)
9. occupancy – percent of the 1971 population who had resided in the same locality for 10 or more years

MORTALITY RATES (n=2)

30. **Vincenti et. al. 2004**

Confounders (total 5)

1. Gender - person years of follow-up
2. Age – 5-year age groups and calendar-year categories
3. Educational attainment (limited to subjects aged 30 or more on 31 December 1985)
   a. elementary or lower
   b. middle school
   c. high school or university
4. Occupation (limited to subjects aged 30-65 on 31 December 1985)
   a. agriculture
   b. industry
   c. other
5. Emigration – (82 subjects, 1.6%)

31. **Yang et. al. 1998**

Confounders (total 3)

1. Urbanisation index
2. Midyear population
   a. by sex
   b. age
   c. calendar year during 1982-1991
3. Chlorinating municipality or non-chlorinating

RATE RATIO (n=1)

32. **Marcus et. al. 1998**

Confounders (total 8)

1. Number of suppliers (of water)
2. Age (years)
3. Percentage black
4. Income
5. Percentage >12 years' education
6. Percentage urban (urban status)
7. Age adjusted breast cancer incidence rates (per 100,000 per year)
8. THM level

INCIDENCE RATES (n=1)

33. **Bean et. al. 1982**

Confounders (total 8)

1. Water source
2. Depth of well
3. Aged standardised cancer rates by sex for each town or selected groups of towns
4. Socioeconomic status by county, township and municipality
5. Occupation
6. Geographical mobility
7. Water usage
8. Smoking patterns

Chapter 4: Discussion

"If the malignant spirits whom we moderns call cholera, typhus and smallpox, were one day to set out in quest of the man who had been, within the past thirty or forty years their deadliest foe in all London, they would probably make their way to St. Mary's, Wimbledon."

This quote, referring to Sir Joseph Bazalgette, epitomizes the magnitude of his work and the affect that it had on London in the mid nineteenth century (Hansen 2016b).

***Sure Cure for Cholera** 2016*

Rehydration is the cornerstone of treatment for cholera (Center for Disease Control and Prevention 2016)

The systematic review and the public debate

This systematic review is the first to consider in detail the association between a known exposure to water disinfected with chlorine and risk of cancers other than bladder and colorectal. This differentiates it from previous studies reviewing the relationship between chlorinated water and cancer. As such, the results provide important information lending weight to public health concerns over CDBs produced from chlorine disinfection of source water supplies and their association with cancer. Exposure to CDBs is now considered widespread and current global rates of cancer incidence and mortality are considered to be at epidemic proportions (American Cancer Society 2016; Servan-Schrieber 2016; Villanueva et al. 2015). Global estimates of absolute cancer incidence and mortality are 182 and 102 per 100,000 population, respectively (IARC 2014).

Controversy over the need for and use of chlorine as a disinfectant is not new. The story of Semmelweis, (Chapter 1), adverse concerns reported by Race in 1918 and more recently the association with THM levels with chlorinated water are testimony to this (Benedek 1983; Best and Neuhauser 2004; Race 1918; Rook 1974). Since then other adverse health

outcomes including reproductive and developmental complications have been associated with exposure to CDBs (Tomasz 2009; USEPA 2015).

Biologically safe water or infectious water disinfected with chlorine?

There were four cholera epidemics recorded in London in the 19th century between 1831 and 1866 (City of Westminster Archives 2016). The first reported death from cholera in Britain was in 1831 when William Sproat of Sunderland contracted the disease and died three days later sparking the first cholera epidemic of London in 1832 (City of Westminster Archives 2016; The Gazette Official Public Record 2016). The remaining three epidemics occurred in 1841, 1854 and the last in 1866 (Hansen 2016b). Throughout the 19th century, the population of London of approximately 3 million people in 1860 and 7 million by the beginning of the 20th century, consumed and bathed in untreated river water sourced mostly from the Thames River. This water was not chlorinated yet it contributed to the overall health and prosperous growth of the city and nation throughout the 19th century. It was not until the beginning of the 20th century that large scale chlorine disinfection of public water supplies began due to sewage contamination and infectious disease risk (City of Westminster Archives 2016; Hansen 2016b; Lemon 2016; Stanwell-Smith 1997; Water Quality and Health Council 2016). Today, raw sewage continues to be discharged into the Thames and works is ongoing to improve and develop the hygienic management and handling of the sewage generated by London's eight million inhabitants (Hansen 2016a).

In the case of public water supplies for large populations, the management of the Thames River as a result of the great stink of 1858 serves as a stark reminder. Population growth results in the need for hygienic waste management to avoid the spread of disease and infectious outbreaks (Lemon 2016). The development of effective sewage management in

London in the 1800's is testimony that water supplies can be safely provided to large populations without the need for large scale chlorine disinfection (Hansen 2016b). Indeed, water has been safely consumed for centuries around the world in large urban population centres without the need for disinfection by protecting the source water from contamination, particularly of sewage (Hansen 2016b; Stanwell-Smith 1997). Large scale disinfection of public water supplies with chlorine renders contaminated and infectious water, non-infectious (Newsom 2006; Water Quality and Health Council 2016). It also produces a range of CDBs some of which can be extremely toxic (Richardson and Postigo 2012; Richardson et al. 2007).

Chlorine disinfection by-products

Complaints about the palatability, and adverse health (and environmental) effects of disinfecting water with chlorine have always existed. They have been largely overlooked because of the overriding success of supplying water rendered non-infectious. Also identified has been the added advantage of eliminating the need for capital investment and development of infrastructure necessary to hygienically manage sewage (Hansen 2016a, b; Race 1918; Water Quality and Health Council 2016).

In 1974, because of the high rates of cancer in New Orleans (US), the association with chlorinated water and cancer was identified by Rook (Rook 1974). The possibility that water disinfected with chlorine could be the basis for adverse health outcomes thrust Rook's work into the public spotlight (DeRoun T. A. 1975), where it has remained, making it an important topic of public health debate. Despite the controversy, the US EPA immediately took action to mitigate exposure to CDBs through enforcing legislation on water quality that was passed in 1974 (Table 3) (USEPA 2004, 2015). Since 1974, the

knowledge base regarding CDBs and adverse health effects has continued to develop. In 1998, Wigle suggested that chlorine disinfected water is potentially one of the most important environmental carcinogens in terms of the number of attributable cancers per year (Wigle 1998). An example, calculated by Malcolm, is the population attributable risk (PAR) for New Zealand in 1995 associated with cancers, estimated to be 329 preventable cancer deaths annually (Malcolm et al. 1999). Using the same calculation for the PAR associated with CDBs and birth defects, Malcolm estimated 94 birth defects per year potentially associated with exposure to CDBs (Malcolm et al. 1999). The issue of CDB exposure is not restricted to cancer and the potential adverse health risk increases when other adverse health outcomes (e.g. reproductive and developmental complications) are also considered (Tomasz 2009; USEPA 2005a; Villanueva et al. 2015). The findings of the present systematic review support these concerns. They also endorse the proactive position taken by the US EPA and others to reduce exposure to CDBs.

Significance of the 12 statistically significant point estimates

Twenty-four articles reported on cancer risks and provided data that could be pooled using meta-analytic methods. These analyses of the original cohort and case control studies returned 12 statistically significant point estimates (Table 3, Chapter 3). Bias was addressed through application of the Joanna Briggs Institute systematic review methodology, assisting to improve overall statistical validity and certainty of the analytical outcomes. The comprehensive literature search identified all relevant studies. Data derived from the included articles was corrected for a wide range of potential confounders by application of appropriate statistics at the time of publication (Supplemental Material Appendix 3). From the meta-analyses presented in Chapter 3, point estimates for lung and non-Hodgkin's lymphoma returned statistically significant predictive intervals, indicating

that for these cancer sites there is possible generalisability to the broader population. This provides additional evidence in support of an association (Table 3, Chapter 3).

The results from the present work support the association between CDBs and cancer originally made by Rook in 1974 (Rook 1974). The 12 statistically significant point estimates add to the weight of evidence already established for bladder and colorectal cancers, and increase the range of cancers associated with CDB exposure. As such, they strengthen the argument for a causal inference (Hrudey and Fawell 2015). Chapter 3 provides a detailed analysis of results that are summarised in Table 3 and 4.

Caveats to applying the results generally are the high degree of heterogeneity observed in the present meta-analysis and non-significant predictive intervals for all but two analyses. Heterogeneity may reflect the wide range and dynamic nature of the variables associated with source water, treatment plant chemistry and possible confounders including new and emerging contaminants. However, a criterion of confirmed CDB exposure was established a priori. While this does not eliminate the effects of CDB profile, it does ensure a CDB dose of concern was present in the water. This value varied based on reported CDB, study and year of study. Heterogeneity is discussed in detail in Chapter 3.

How big is the problem?

An overall relative increased risk of 13% for all reported cancers pooled across all geographical regions, for both genders, (Figure 3, Table 3, Chapter 3) was observed. The associated range of absolute effect in cancer incidence and mortality for all reported cancers and geographical regions is 1% (Female: all cancers) to 31% (Asia: all cancers) and for specific cancers 3% (Female Reproductive and Melanoma) to 113% (Melanoma).

Statistically significant increased relative risk was also returned for men and women, and in five specific cancer sites including breast, female reproductive, lung, melanoma and non-Hodgkin's, as well as for geographical regions including North America and Europe (Table 4, Chapter 3). The results overlay neatly with the leading global cancer incident statistics reporting, breast, female reproductive, melanoma and lung all ranked in the top five cancers globally (IARC 2014). The results for lung and non-Hodgkin's cancer returned low within and between study measures of heterogeneity and statistically significant predictive intervals adding further strength to the evidence for an association between exposure to water disinfected with chlorine and cancer.

Lung cancer and melanoma

More recently, inhalation and dermal exposure are being considered as important, if not more important, routes of exposure compared with ingestion (Leavens et al. 2007; Villanueva and Font-Ribera 2012). The basis for this is the volatile nature of many CDBs and the use of water for bathing. The possibility that lung and melanoma cancer sites may be associated with CDBs exposure indicates a need for further study into this area, and exposure routes other than ingestion. Recently the United Nations has established target 10 millennium development goals to expedite the provision of sanitary water and reduce the incidence of infectious outbreaks. However, reliance on chlorine disinfection to make water non-infectious may have the unintended effect of increasing exposure to CDBs (Pruss-Ustun A 2008). Therefore, water infrastructure programs should take a holistic approach to ensure water is safe. This does not eliminate chlorination but places chlorination as a security measure if the water supply becomes infectious.

Breast, female reproductive, and non-Hodgkin's (including bladder and colorectal) cancers: Why these specific cancers?

Cancers, associated with exposure to chlorinated water occurring in certain parts of the body and not others, is an area requiring additional knowledge and research (Villanueva et al. 2014). Body systems associated with transporting and cycling water or removing waste may predicate toxic exposure and bio-accumulation of CDBs within certain cell or tissue sites. The body is primarily water based and reliant on fluid circulation to maintain health (Langley et al. 2015; Thongboonkerd 2007). As such, the role of the bladder and colorectal sites are closely related to water movement and waste elimination and would appear logically to have an association. It may explain why they have appeared first and most consistently in the research (USEPA 2015). Similarly, sites identified in the present review as having an association with CDB exposure could be explained in the same way. That is, the relationship of each system in connection with fluid circulation and waste removal within the body.

It can be hypothesised that the lymphatic system would appear to be a logical tissue where cancer associated with water movement and waste removal might be observed. Breast, female reproductive, (dominated by ovarian cancer) and non-Hodgkin's lymphoma each have substantial relationship with lymph circulation (Thongboonkerd 2007). Non-Hodgkin's lymphoma is lymph based and this in addition to lung cancer had the strongest statistical evidence of a causal inference.

The burgeoning chemical burden: Organics of natural and anthropogenic origin

Hygienic management of sewage in 19th century London eliminated dysenteric epidemics especially of cholera and typhoid. It demonstrated that large urban populations could

prosper substantially without the need to disinfect water with chlorine (City of Westminster Archives 2016; Hansen 2016b; Lemon 2016). London's population in 1860 was approximately 3 million people and approaching 7 million at the beginning of the 20th century before chlorine disinfection was introduced (Old Bailey Proceedings Online 2016).

Chlorine disinfection became popular because it could make water contaminated with sewage non-infectious and achieve this inexpensively (Water Quality and Health Council 2016). However, enabling consumption of water contaminated with sewage in this way compounds the organic burden in water. Potentially increasing the CDB load through provision of precursors. This may explain the discovery of the relationship between increased cancer rates and THMs in the Mississippi River in New Orleans (Rook 1974). At this point extensive reclamation and discharge of both chlorine-treated water and raw sewage would have occurred repeatedly with accumulation of environmental CDBs (Rook 1974). The pattern of concentrating organic precursors and CDBs from sewage contaminated and chlorine disinfected water occurs in every major water way around the world where water treatment plants are established (Villanueva et al. 2015).

It appears the toxicity issue associated with naturally occurring organics (distinct from anthropogenic) primarily arises through their chlorination. Indeed, Thames River water throughout the 18th century was likely to have had a high naturally occurring organic load. This could have potentially supplied beneficial (probiotic) organisms and natural prebiotics to maintain the microbiome of humans (National Institute of Health 2016). This may help explain how Londoner's were able to successfully consume Thames River water throughout the 18th century as well as in the centuries preceding this without succumbing to infectious epidemics (Johnson 2016). This would have combined with the hygienic

management of sewage, as is demonstrated by the success of the embankment project in London (Hansen 2016b; Lemon 2016).

The environmental organic burden is increasing. Clark and co-workers in 1986 documented the dramatic increase in the global environmental chemical burden caused by anthropogenic activity. In just 30 years between 1956 and 1986, the chemical output increased 10 fold from 5 to 50 billion tonnes per year (Clark et al. 1986). The rate of production and introduction of new chemicals into the environment has not abated and today, the chemical abstract service (CHEMLIST) lists 345,000 regulated chemicals globally, with 50 new chemicals a week being added to this list (Chemical Abstract Service 2016). The range of new chemicals entering the water supply not only increases the range of CDBs produced, but increases the likelihood of adverse health outcomes as well (Sjerps et al. 2016). It also adds a layer of confounding which complicates the identification of causal associations between the potential causative agent and disease outcomes (Richardson and Postigo 2012; Richardson et al. 2007). The baseline CDB profile will have changed because of increased organic load and changes to chlorine treatment protocols. This will impact non-communicable diseases including those with potentially long latency; for example, some cancers.

Cost of inactivity

In 2006 the US EPA estimated that 280 cases of bladder cancers are avoidable. This includes 207 non-fatal and 73 fatal cases avoided as a result of reductions to CDBs exposure introduced in the 2006 stage 2 disinfection by-product rules. Avoidance would result in savings of $763 million to $1.5 billion and improve social outcomes as well (USEPA 2006b). Extrapolation of this figure to our results indicates the savings in

healthcare expenditure is substantial. Compounded by this is the possibility of other serious adverse health outcomes (e.g. reproductive and developmental complications), which have also been linked with CDB exposure (Tomasz 2009; USEPA 2005a, 2015).

Conclusion

Our results do affirm and add further to the evidence established for bladder and colorectal cancers and the association with CDBs. However, the high degree of heterogeneity consistently observed both within and across studies over the last 40 years prevent making this a definitive conclusion. Heterogeneity within and across studies remains a feature of the research into CDBs and risks to health and is explained by the many variables. Researchers have attempted to account and adjust for these. However, the changing organic load and chlorine treatment regimens may increase the confounder effects. As such, many CDBs remain unidentified and contribute to the difficulty of elucidating CDB exposure patterns and cancer incidence and mortality.

Given the complexity of environmental exposures attempts to identify the causal agents will have limited return. The issue is establishing or refining risk assessment models for practical application in the field. Our results support the findings of the US EPA and their ongoing decisions to reduce exposure to CDBs (USEPA 2015). The objective is the provision of safe water to the end user; as such, consideration of health risks beyond infectious agents should be a public health concern. This extension should include all water uses given the significance of dermal and inhalation routes for CDB exposure.

Recommendations for best practice

It is unlikely disinfection of water with chlorine will cease anytime in the foreseeable future despite the escalating concern and potential for adverse health outcomes associated

with exposure to CDBs. This is because chlorine has been successfully used in preventing infectious outbreaks of dysenteric diseases where water supplies are contaminated and infectious. This has been driven by the fear of such outbreaks and apparent ease of chlorination to provide an insurance (Water Quality and Health Council 2016). It largely ignores evidence that large populations have consumed water safely over many centuries without the need for disinfection with chlorine; a good example of this is London's experience in the 19th century.

Infection control versus chlorine disinfection by-product exposure

It has been almost one hundred years since Race documented the first descriptions of adverse health outcomes associated with the by-products of chlorination (Race 1918). He first published at the beginning of large scale chlorination of public water supplies. It is also more than 40 years since Rook made the potential link between CDBs and cancer in 1974 (Rook 1974). Despite the encouraging action of the US EPA which acted urgently in 1974 as a result of Rooks discovery (Table 3). The overwhelming attitude towards disinfection of water supplies with chlorine, by the water industry generally, and public health advocates remains one of, "infection control is paramount and in no way should be compromised to lower exposure risk to CDBs" (American Water Works Association 2011; NHMRC 2011; WHO 2011). Malcolm in 1999, (Malcolm et al. 1999), Wigle in 1998 (Wigle 1998) and others including the US EPA (USEPA 2005a) have highlighted the need, for many years now that exposure to CDBs constitutes a risk to health. This is a risk that increases the burden not only of chronic disease within communities but also the cost to manage this disease. The results from this systematic review help to put scale and magnitude to the potential size of the problem. Ongoing research will help to clarify the many areas where lack of understanding prevents definitive choices of what further action

is necessary. Research will define the action and their sequence to continue to ameliorate and mitigate adverse health outcomes of CDB exposure without negatively affecting infection control.

Improvements in research design and analysis: A move to causal inference

Improvements in epidemiological study designs to include Direct Acyclic Graphs (DAGs) analysis and propensity scores will help support the assumption of causality and further refine the causal nature of the relationship (Austin 2011; Weisskopf et al. 2015). Hrudey states that consistency of an association, even with epidemiological studies can still provide useful evidence to inform a causal inference (Hrudey et al. 2015). Villanueva and co-workers have reviewed the state of knowledge in assessing exposure to chemicals in drinking water and health consequences and lists in detail the knowledge gaps and areas of research necessary to address these (Villanueva et al. 2014).

Joanna Briggs Institute: Levels of evidence and grades of recommendation

This systematic review has followed the Joanna Briggs Institute (JBI) approach, designed to improve overall quality of research outcomes and includes the JBI levels of evidence and grades of recommendations (The Joanna Briggs Institute 2016). As such, a systematic review of the "best available evidence" which, due to the nature of epidemiological research, results in the assessment of cohort and case control study designs. Critical review of the selected papers resulted in an overall rating of high quality and was the source of data used in meta-analysis (Chapter 3 and Supplemental Material, Appendix 2). As has been previously stated, the high degree of heterogeneity returned from MA and statistical analysis (Table 3, Chapter 3) prevents making a definitive statement of causality. However, because of the number, frequency and consistency of statistically significant

associations made since Rook's defining study of 1974, this is basis for a causal inference derived from the existing pool of epidemiological research (Hrudey et al. 2015; Rook 1974; USEPA 2015). It is also the basis for action taken by the US EPA since 1974 to intervene in the interest of public health (USEPA 2015).

Accordingly, and on the basis of twelve statistically significant point estimates derived in this systematic review, two of which returned statistically significant predictive intervals a Grade A or "strong" determination within the JBI grades of recommendations has been made (The Joanna Briggs Institute 2016). It is clear the desirable effects of mitigating exposure to CDBs outweigh the adverse health effects, in this case cancer associated with exposure to water disinfected with chlorine.

First step: Acknowledge the problem

The first step towards best practice is acknowledging there is a problem. The US EPA has set the best example for this and despite the controversy dating from 1974 has been proactive and set the benchmark for regulating CDBs to reduce population risk and exposure (USEPA 2015). The rest of the world follows. Governments, healthcare agencies and policy makers may now prioritise water treatment policy and recommendations given the potential for health gains and reductions in chronic disease burdens across communities as a result.

Ongoing research is required to continue to define the balance for the need for chlorination and disinfection of source waters, and exposure to CDBs and to identify new methods of supplying water safely to consumers. The hygienic management of sewage to prevent contamination of water supplies will help mitigate the need for disinfection. Also, research

to determine the most desirable water qualities for health will help set the gold standard to strive for in the entire water supply chain. The challenge is how to deliver this quality of water to end users.

Meanwhile, the WHO has created a register for household water treatment systems in order to help identify effective systems for treating, filtering and storing water safely. These include point-of-use processes; for example, filtering and boiling water. For immediate protection, point-of-use controls have been identified as effective steps to ameliorate and control dysenteric outbreaks particularly in areas where contaminated or infectious water supplies exist as well as for reducing exposure to CDBs and other potentially toxic anthropogenic chemicals (WHO 2014, 2016). This includes point-of-use filtration to remove CDBs and other contaminants from water which remains an important and popular method for individuals to reduce exposure and risk of adverse health outcomes either perceived or real.

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Appendices

1. Papers Excluded after Critical Appraisal n=13
2. Papers excluded after detailed examination n=41
3. Papers Excluded for Bowel and Bladder Cancer n=34
4. Additional Meta-analysis plots (Chapter 3)
5. Statement of Authorship

Appendix 1: Papers excluded after critical appraisal (n=13)

No eligble data to extract (n =2)

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Bowel / Bladder Cancer (n=1)

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Not Relevant (n=1)

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Appendix 2: Papers excluded after detailed examination (n=41)

Review Article/Conference Proceedings/Commentary (n=23)

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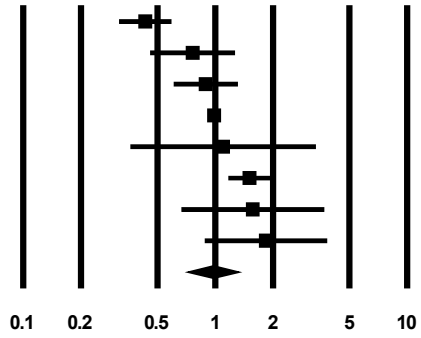
Appendix 4: Additional meta-analysis plots (Chapter 3)

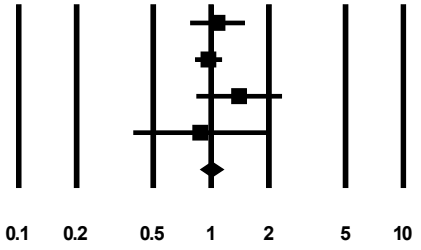
Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Vinceti et. al. 2004	0.432	0.318	0.587	0.000	15.75
Fagliano 1998	0.763	0.462	1.260	0.291	12.41
Gottlieb et. al. 1982	0.893	0.612	1.303	0.557	14.54
Koivusalo et. al. 1997	0.986	0.925	1.051	0.665	18.63
Wilkins 1981	1.100	0.365	3.318	0.866	5.39
Cantor et. al. 1999	1.512	1.178	1.941	0.001	16.66
Young 1983	1.570	0.671	3.674	0.298	7.59
Gottlieb & Carr. 1982	1.838	0.888	3.806	0.101	9.03
	0.979	0.722	1.326	0.889	



Heterogeneity: Q = 42.7 df = 7, $p < 0.01$, $I^2 = 84.2$, $Tau^2 = 0.128$

Figure App4.1: Brain and nervous tissue cancers, impact of exposure to chlorine disinfection by-products on incidence and mortality risk.

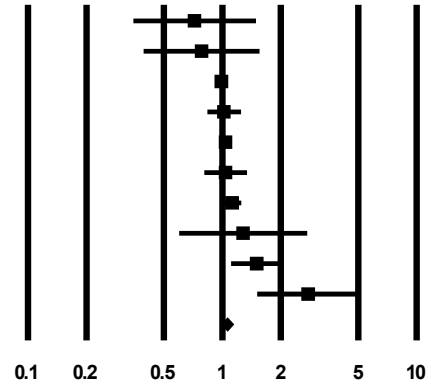
Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Gottlieb et. al. 1982	1.080	0.784	1.488	0.638	17.03
Koivusalo et. al. 1997	0.970	0.831	1.132	0.699	73.38
Vinceti et. al. 2004	1.400	0.844	2.322	0.192	6.83
Wilkins 1981	0.880	0.397	1.949	0.753	2.76
	1.010	0.885	1.153	0.880	



Heterogeneity: Q = 2.2 df = 2, $p = 0.54$, $I^2 = 0.00$, $Tau^2 = 0.000$

Figure App4.2: Prostate cancer, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Young 1983	0.720	0.351	1.476	0.370	0.86
Wilkins 1981	0.781	0.397	1.537	0.475	0.96
Brenniman 1979	0.989	0.979	0.999	0.027	30.46
Tsai et. al. 2013	1.020	0.843	1.234	0.839	8.86
Koivusalo et. al. 1994	1.039	1.000	1.079	0.052	27.93
Gottlieb et. al. 1982	1.040	0.814	1.329	0.755	6.05
Koivusalo et. al. 1997	1.122	1.017	1.239	0.022	18.44
Doyle et. al. 1997	1.280	0.605	2.706	0.519	0.79
Vinceti et. al. 2004	1.504	1.119	2.022	0.007	4.43
Tao et. al. 1999	2.770	1.523	5.039	0.001	1.22
	1.062	0.992	1.136	0.082	



Heterogeneity: Q = 32.5 df = 9, $p < 0.01$, $I^2 = 72.2$, $Tau^2 = 0.000$

Figure App4.3: Upper gastrointestinal tract (Oesophageal, Stomach and Small intestine), impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Gottlieb et. al. 1982	0.861	0.571	1.298	0.474	13.48
Brenniman 1979	0.989	0.979	1.000	0.045	32.83
Tsai et. al. 2013	1.020	0.843	1.234	0.839	25.09
Koivusalo et. al. 1997	1.325	0.982	1.787	0.066	18.63
Wilkins 1981	1.760	0.434	7.135	0.429	1.86
Tao et. al. 1999	2.770	1.523	5.039	0.001	8.11
	1.135	0.933	1.382	0.206	

Heterogeneity: Q = 16.2 df = 5, $p < 0.01$, $I^2 = 69.0$, $Tau^2 = 0.030$

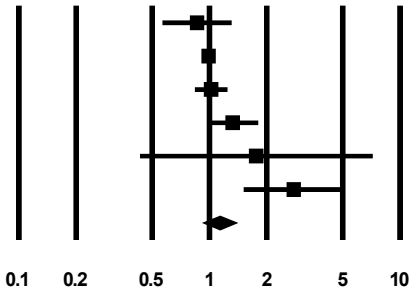


Figure App4.4: Oesophageal cancer, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Wilkins 1981	0.610	0.282	1.321	0.210	0.73
Young 1983	0.720	0.351	1.476	0.370	0.84
Brenniman 1979	0.984	0.954	1.016	0.333	35.64
Koivusalo et. al. 1994	1.039	1.000	1.079	0.052	34.39
Koivusalo et. al. 1997	1.100	0.990	1.221	0.076	19.72
Gottlieb et. al. 1982	1.154	0.850	1.567	0.357	4.21
Vinceti et. al. 2004	1.504	1.119	2.022	0.007	4.47
	1.045	0.978	1.117	0.193	

Heterogeneity: Q = 17.2 df = 6, $p < 0.01$, $I^2 = 65.2$, $Tau^2 = 0.030$

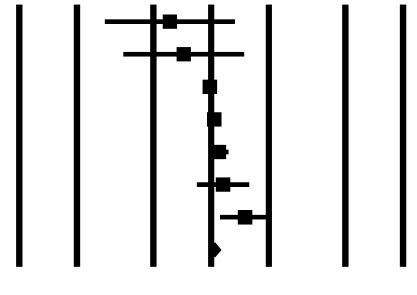


Figure App4.5: Stomach cancer, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Young 1983	0.710	0.357	1.410	0.328	8.05
Brenniman 1979	1.014	0.943	1.089	0.711	20.88
Koivusalo et. al. 1997	1.082	0.915	1.279	0.356	19.36
Gottlieb et. al. 1982	1.189	0.793	1.782	0.402	13.53
Vinceti et. al. 2004	1.383	0.793	2.410	0.253	10.24
Koivusalo et. al. 1995	1.576	1.476	1.683	0.000	20.94
Wilkins 1981	1.627	0.756	3.499	0.213	6.98
	1.193	0.932	1.527	0.162	

Heterogeneity: Q = 86.6 df = 6, $p < 0.01$, $I^2 = 93.0$, $Tau^2 = 0.075$

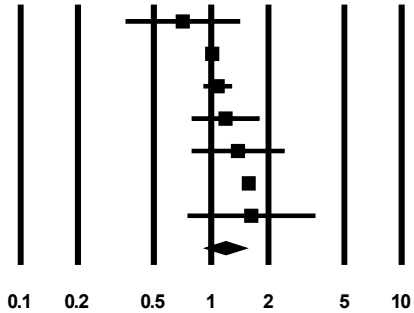


Figure App4.6: Liver and Gallbladder cancers, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Statistics for each study				
	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Young 1983	0.710	0.357	1.410	0.328	8.46
Brenniman 1979	1.004	0.931	1.083	0.917	20.86
Gottlieb et. al. 1982	1.189	0.793	1.782	0.402	13.92
Koivusalo et. al. 1997	1.225	0.956	1.569	0.109	17.75
Vinceti et. al. 2004	1.383	0.793	2.410	0.253	10.67
Koivusalo et. al. 1995	1.576	1.476	1.683	0.000	20.96
Wilkins 1981	1.627	0.756	3.499	0.213	7.37
	1.219	0.942	1.576	0.132	

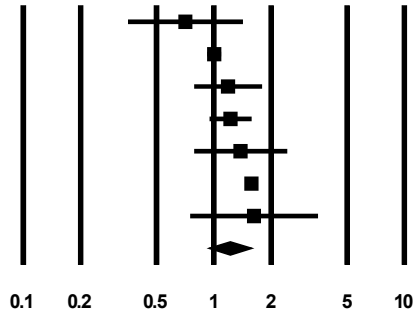


Figure App4.7: Liver cancer, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Statistics for each study				
	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight weight
Koivusalo et. al. 1997	0.975	0.776	1.224	0.825	49.74
Brenniman 1979	1.104	0.880	1.384	0.392	50.26
	1.038	0.884	1.218	0.652	

Heterogeneity: Not applicable

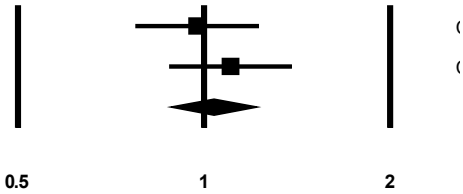


Figure App4.8: Gallbladder and ducts cancers, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Statistics for each study				
	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Kukkula et. al. 1997	0.400	0.241	0.662	0.000	3.76
Wilkins 1981	0.750	0.404	1.394	0.363	2.70
Do et. al. 2005	0.904	0.842	0.972	0.006	15.62
Koivusalo et. al. 1997	1.007	0.878	1.155	0.918	13.32
Chiu et. al. 2010	1.010	0.847	1.205	0.912	11.76
Brenniman 1979	1.023	1.008	1.038	0.003	16.66
Gottlieb et. al. 1982	1.030	0.760	1.397	0.848	7.41
Young 1983	1.140	0.692	1.877	0.606	3.83
Koivusalo et. al. 1995	1.232	1.178	1.287	0.000	16.28
Vinceti et. al. 2004	1.276	0.783	2.080	0.327	3.96
Ijsselmuiden 1992	3.252	2.105	5.024	0.000	4.70
	1.056	0.945	1.180	0.340	

Heterogeneity: Q = 117.3 df = 10, $p < 0.01$, $I^2 = 91.5$, $Tau^2 = 0.019$

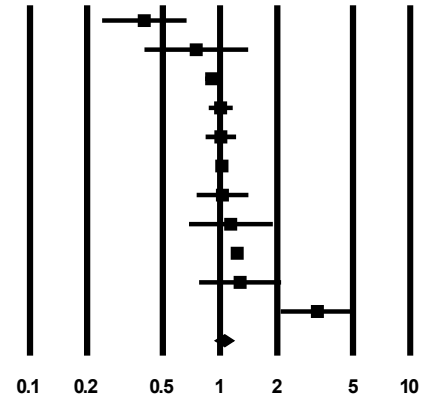


Figure App4.9: Pancreatic cancer, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Vinceti et. al. 2004	0.403	0.311	0.523	0.000	11.66
Young 1983	0.630	0.281	1.414	0.263	5.38
Brenniman 1979	0.976	0.886	1.075	0.616	13.20
Liao et.al. 2012	0.980	0.769	1.249	0.870	11.87
Koivusalo et. al. 1997	1.033	0.892	1.196	0.665	12.85
Wilkins 1981	1.099	0.483	2.500	0.821	5.27
Doyle et. al. 1997	1.110	0.473	2.603	0.811	5.04
Koivusalo et. al. 1998	1.313	1.079	1.597	0.006	12.39
Gottlieb et. al. 1982	1.407	0.883	2.242	0.150	8.98
Koivusalo et. al. 1994	1.493	1.406	1.584	0.000	13.37
	0.996	0.782	1.268	0.974	

Heterogeneity: Q = 145.3 df = 9, $p < 0.01$, $I^2 = 93.8$, $Tau^2 = 0.113$

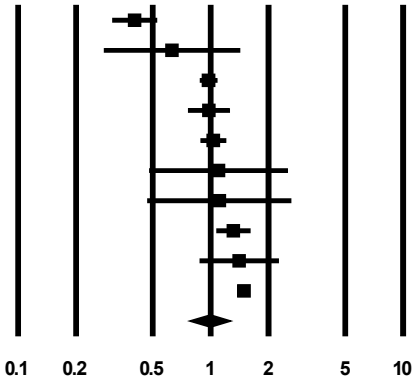


Figure App4.10: Urinary tract cancers, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Vinceti et. al. 2004	0.403	0.311	0.523	0.000	13.15
Young 1983	0.630	0.281	1.414	0.263	6.92
Liao et.al. 2012	0.980	0.769	1.249	0.870	13.34
Koivusalo et. al. 1997	1.033	0.892	1.196	0.665	14.17
Wilkins 1981	1.099	0.483	2.500	0.821	6.80
Doyle et. al. 1997	1.110	0.473	2.603	0.811	6.53
Koivusalo et. al. 1998	1.313	1.079	1.597	0.006	13.78
Gottlieb et. al. 1982	1.407	0.883	2.242	0.150	10.70
Koivusalo et. al. 1994	1.493	1.406	1.584	0.000	14.60
	0.996	0.744	1.335	0.980	

Heterogeneity: Q = 116.1 df = 8, $p < 0.01$, $I^2 = 93.1$, $Tau^2 = 0.153$

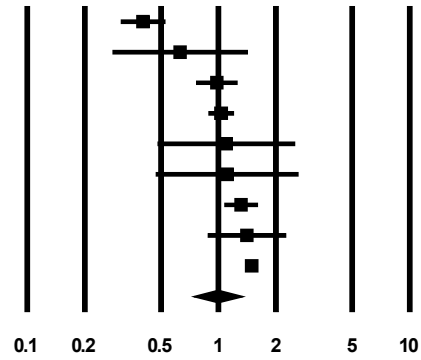


Figure App4.11: Kidney cancer, impact of exposure to chlorine disinfection by-products on incidence and mortality risk

Study name	Risk (RI)	95% CI lower	95% CI upper	p	Relative weight
Gottlieb et. al. 1982	0.912	0.508	1.639	0.758	6.53
Koivusalo et. al. 1997	0.973	0.763	1.242	0.827	27.67
Koivusalo et. al. 1995	1.193	1.087	1.308	0.000	65.80
	1.108	0.948	1.295	0.198	

Heterogeneity: Q = 3.0 df = 2, $p = 0.23$, $I^2 = 32.8$, $Tau^2 = 0.007$

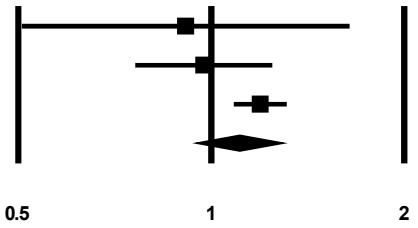


Figure App4.12: Hodgkin's lymphoma, impact of exposure to chlorine disinfection by-products on incidence and mortality risks

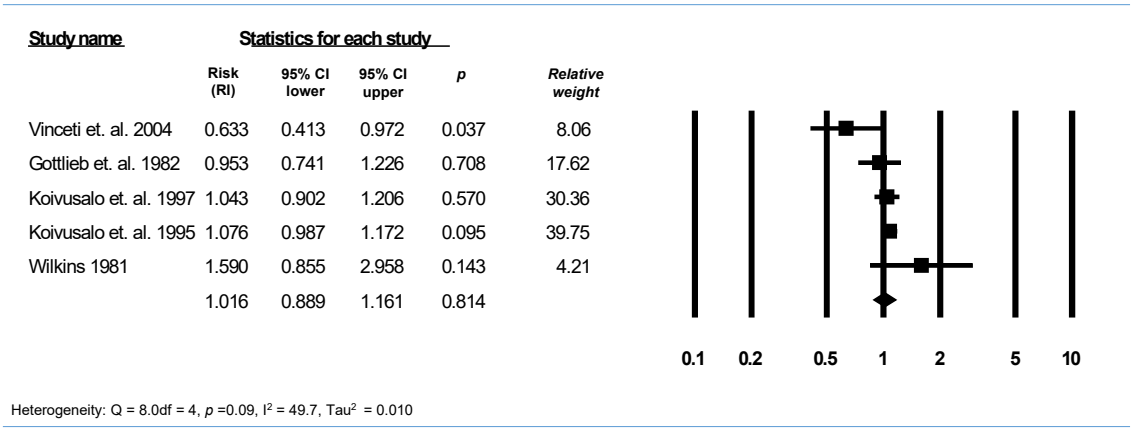


Figure App4.13: Leukaemia, impact of exposure to chlorine disinfection by-products on incidence and mortality risks

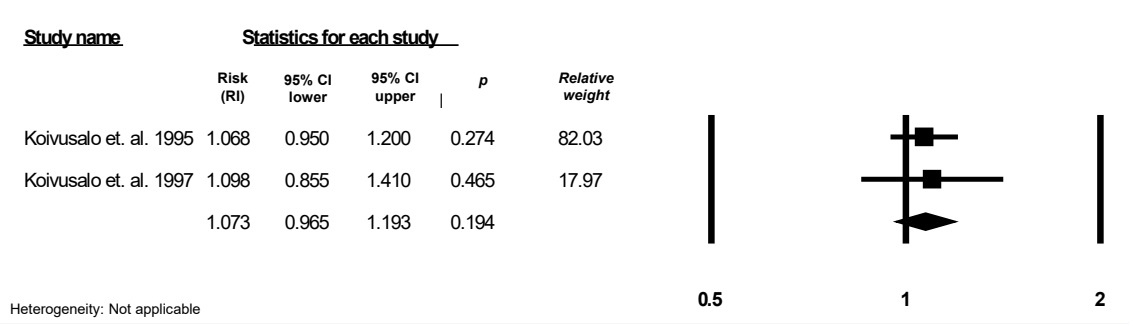


Figure App4.14: Soft tissue cancers, impact of exposure to chlorine disinfection by-products on incidence and mortality risks

Appendix 5: Statements of authorship.

Statement of Authorship

Title of Paper	Chlorinated water and overall risk of cancer: A systematic review.
Publication Status	Submitted for publication 23 March 2016, at review stage.
Publication Details	Environmental Health Perspectives

Principal Author

Name of Principal Author (Candidate)	Gordon David Parbery		
Contribution to the Paper	Conception and design; analysis and interpretation of data; writing and critically reviewing the manuscript; gave final approval of the version to be published; acted as corresponding author.		
Overall percentage (%)	95%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24 March 2016

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr David Tivey		
Contribution to the Paper	Supervised development of work; provided guidance regarding amendments to the original systematic review protocol; helped to evaluate and edit the manuscript; gave final approval of the version to be published.		
Signature		Date	24 March 2016

Name of Co-Author	Ms. Alexa McArthur		
Contribution to the Paper	Helped to evaluate, structure, critically review and edit the manuscript; gave final approval of the version to be published.		
Signature		Date	24 March 2016

Statement of Authorship

Title of Paper	Epidemiological association between chlorinated water and overall risk of cancer: A systematic review.
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Publication Details	Parbery G, Tivey D, McArthur A. 2012. Epidemiological association between chlorinated water and overall risk of cancer: A systematic review. The JBI Database of Systematic Reviews and Implementation Reports 10:259-272.

Principal Author

Name of Principal Author (Candidate)	Gordon David Parbery		
Contribution to the Paper	Literature searching and synthesis of systematic review protocol.		
Overall percentage (%)	95%		
Certification:	This paper reports on the background leading to the systematic review including a description of the Joanna Briggs Institute methodology for conducting systematic reviews.		
Signature		Date	24 March 2016

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr David Tivey		
Contribution to the Paper	Supervised development of protocol for systematic review protocol.		
Signature		Date	24 March 2016

Name of Co-Author	Ms. Alexa McArthur		
Contribution to the Paper	Helped to evaluate, structure, critically review and edit the protocol for publication.		
Signature		Date	24 March 2016