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Review

Assessing the human health impacts of exposure to disinfection by-products — A critical review of concepts and methods ☆

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ABSTRACT

Understanding the public health implications of chemical contamination of drinking water is important for societies and their decision-makers. The possible population health impacts associated with exposure to disinfection by-products (DBPs) are of particular interest due to their potential carcinogenicity and their widespread occurrence as a result of treatments employed to control waterborne infectious disease.

We searched the literature for studies that have attempted quantitatively to assess population health impacts and health risks associated with exposure to DBPs in drinking water. We summarised and evaluated these assessments in terms of their objectives, methods, treatment of uncertainties, and interpretation and communication of results.

In total we identified 40 studies matching our search criteria. The vast majority of studies presented estimates of generic cancer and non-cancer risks based on toxicological data and methods that were designed with regulatory, health-protective purposes in mind, and therefore presented imprecise and biased estimates of health impacts. Many studies insufficiently addressed the numerous challenges to DBP risk assessment, failing to evaluate the evidence for a causal relationship, not appropriately addressing the complex nature of DBP occurrence as a mixture of chemicals, not adequately characterising exposure in space and time, not defining specific health outcomes, not accounting for characteristics of target populations, and not balancing potential risks of DBPs against the health benefits related with drinking water disinfection. Uncertainties were often poorly explained or insufficiently accounted for, and important limitations of data and methods frequently not discussed. Grave conceptual and methodological limitations in study design, as well as erroneous use of available dose–response data, seriously impede the extent to which many of these assessments contribute to understanding the public health implications of exposure to DBPs. In some cases, assessment results may cause unwarranted alarm among the public and potentially lead to poor decisions being made in sourcing, treatment, and provision of drinking water. We recommend that the assessment of public health impacts of DBPs should be viewed as a means of answering real world policy questions relating to drinking water quality, including microbial contaminants; that they should be conducted using the most appropriate and up-to-date data and methods, and that associated uncertainties and limitations should be accounted for using quantitative methods where appropriate.

Contents

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1. Introduction

Maintaining high microbial quality of drinking water is a cornerstone of public health, and chemical disinfection with chlorine and its compounds commonly forms a key component in drinking water treatment. Disinfection by-products (DBPs) may result from reactions between disinfectants and impurities in source water and their occurrence has been a public health concern for the last four decades.

DBPs were first identified in the form of trihalomethanes (THMs) (Bellar et al., 1974; Rook, 1974). By concentration, THMs represent the most prevalent group of DBPs in typical chlorinated drinking water, but many hundreds of other DBPs also occur (Nieuwenhuijsen et al., 2000a; WHO, 2006), several of which are potentially carcinogenic (Richardson et al., 2007). The ~600 DBPs that have been identified (Richardson, 1998; Richardson et al., 2007) represent only a small fraction of the total organic halides present in chlorinated supplies (USEPA, 1998), and relatively few of those chemicals have been adequately characterised in terms of occurrence. Fewer still have been assessed in terms of their potential effects on human health (Richardson et al., 2007).

The occurrence of DBPs has become an issue of interest to policy makers, drinking water providers and engineers, epidemiologists, biologists and risk assessors, particularly since they are a side effect of disinfection with chlorine, which commonly plays an important role in minimising public health risks of waterborne infectious diseases. The concentrations of DBPs vary temporally and geographically according to the physicochemical properties of source water, the nature of treatment and distribution systems, and climate (Amy et al., 2000; Nieuwenhuijsen et al., 2000b), which makes characterisation of general population exposures for the purposes of epidemiological studies and population health impact assessments complex.

Epidemiological studies based on routine monitoring data (e.g. THM concentrations measured at individual residences as a proxy for an unknown putative agent in the DBP mixture) have been carried out for several cancers and several non-cancer health endpoints, in particular birth outcomes (Nieuwenhuijsen et al., 2013). Various systematic reviews, meta-analyses and pooled analyses of cancer studies have also been produced (Amy et al., 2000; Cantor, 1997; Morris et al., 1992; Nieuwenhuijsen et al., 2009a; Villanueva et al., 2003), these show no consistent evidence of associations between DBP exposure and the majority of cancers (Amy et al., 2000). Consistent, positive associations have been found only for bladder cancer: meta- and pooled analyses have demonstrated exposure–response relationships between average residential THM concentrations and bladder cancer in men (Costet et al., 2011; Villanueva et al., 2003, 2004). In terms of non-cancer outcomes, small positive associations have been reported for still births (Nieuwenhuijsen et al., 2010), small for gestational age (Grellier et al., 2010) and congenital anomalies (Nieuwenhuijsen et al., 2009b). For all of these health outcomes, epidemiological evidence is currently not sufficient to infer whether such associations are causal.

Regulatory limits for DBPs have been developed chiefly from data derived from animal toxicological studies. EU guidelines specify a parametric value of 100 μg/L for the four most prevalent THMs (THM4) (European Commission, 1998); the maximum contaminant level in the US is currently 80 μg/L for THM4 (USEPA, 1998). Five haloacetic acids are also regulated in the US, as well as bromate and chlorite (USEPA, 2013). In each case, limits have been set according to available scientific knowledge and account was taken of the precautionary principle, such that life-long consumption of water meeting the guideline values should afford the public protection from adverse health effects. However, cytotoxicological and genotoxicological studies of currently unregulated DBPs indicate that many may be considerably more toxic to humans than THMs or HAAs (Plewa and Wagner, 2009; Plewa et al., 2004, 2008; Richardson et al., 2007). Although THMs make up a high proportion of DBPs in chlorinated drinking water by concentration, it is plausible that, as more data become available on the occurrence and carcinogenicity of some of these unregulated DBPs, the relevance of THMs as a carcinogenic risk factor will diminish considerably (Bull, 2012).

Risk assessment carried out with the aim of determining regulatory limits involves extensive review of both epidemiological and toxicological data. Animal studies tend to be relied upon for providing quantitative dose–response data. Measures of cancer potency—referred to as either potency factors (PF) or slope factors (SF)—are derived by modelling animal carcinogenicity data for each applicable exposure pathway (ingestion, inhalation and dermal absorption) for the most sensitive cancer endpoint. For a suspected genotoxic carcinogen, it is assumed that exposure at any level increases the probability of cancer. The linearised multistage (LMS) model (Crump, 1984) has been used extensively as the default means of extrapolating from the high doses used in animal studies to the lower doses typically experienced by humans. Usually, cancer potency factors are defined using the 95% upper bound of the LMS regression line so as to allow for uncertainties resulting from extrapolation from animals to humans, and from differences in the exposure regimes. In order to calculate regulatory limits, lifetime exposure of a typical human to a potential carcinogen in drinking water is then estimated via each applicable exposure pathway (drinking, washing, showering etc.). An upper bound estimate of lifetime excess cancer risk (LECR)—the lifetime probability of a typical individual developing a cancer—is then estimated by summing the products of exposure through each route by its appropriate potency factor, according to the procedure described by Chrostowski (1994), Gratt (1996) and USEPA (2002a):

$$\mathrm{LECR} = \sum \mathrm{LAE_i} \times \mathrm{PF_i}$$

where LAE is the lifetime average exposure (mg), PF is the potency factor ($(\mathrm{mg/kg\text{-}day})^{-1}$), and i is the exposure route (ingestion, inhalation and absorption). Since the LECR is based on potency factors derived from the upper bound of the LMS model, it can be considered a conservative overestimate that should be protective of public health. Regulatory guidelines use this information to set a concentration of a chemical in drinking water at which the lifetime risk of cancer is considered acceptable (commonly between 1×10^{-4} and 1×10^{-6}, depending on circumstances).

Non-carcinogenic health risk is quantified as a hazard quotient (HQ), calculated from the same estimate of LAE divided by a reference dose (RfD), which is a measure of the potential of a systemic toxic effect in a lifetime of exposure, again commonly derived from animal data. In contrast to genotoxic carcinogenic effects, systemic effects are considered to occur only above an identifiable threshold of exposure at which the body's capacity to detoxify an agent through homeostasis and adaptive mechanisms is exceeded. In order to derive an RfD from animal data, it is necessary, firstly, to identify the no observed adverse effect level (NOAEL), the dose at which no biologically or statistically significant effects are observed in study animals. To estimate a level at which human health is protected, the NOAEL is then divided by a number of uncertainty factors (each typically equal to 10), to account for: (a) variation in sensitivity between among members of the human population; (b) uncertainty involved in extrapolating from animal data to humans; and (c) for extrapolation from subchronic assays to chronic exposure conditions. The RfD can thus be considered the threshold of exposure at which there is no appreciable risk of deleterious systemic effects over a lifetime. Hence, an HQ of less than unity indicates that an individual should not experience adverse non-carcinogenic health effects.

Outside of the regulatory sphere, there are other decision-making contexts in which it is useful to estimate the health impacts associated with exposure to environmental exposures as accurately as possible, without employing conservative, public health-protective assumptions. For the purposes of this review, we broadly refer to such efforts as *population health impact assessments*, although many other terms have been used to describe such studies (Briggs, 2008). Over the last few decades, several studies have been carried out with population health impact assessment as an aim, but which utilise methods and data developed for regulatory risk assessment. Conspicuously fewer population health impact assessments have been done using epidemiological data, or for the purposes of looking at benefits of disinfection versus possible health risks associated with resultant DBPs.

1.1. Aims and objectives

We sought to identify and describe published studies that aim to estimate population health impacts related to exposure to DBPs, with a view to assessing how well this objective has been met in the literature to date. Our specific objectives were to identify the methods used to quantify health risks and impacts, to review the means by which various types of uncertainty were accounted for, and to discuss the ways in which results of such assessments have been interpreted, contextualised, and presented (risk communication). We aimed to provide recommendations for the improvement of population health impact assessment related to exposure to DBPs, and to environmental stressors more generally.

2. Materials and methods

A literature search was carried out to identify studies claiming to assess population health impacts of exposure to DBPs in drinking water (search method presented in Supplementary material 1). Studies were considered eligible if they presented quantitative predictions of health impact or health risk associated with exposure to DBPs for an identified human population. We reviewed all identified studies in detail and their main features were summarised, focusing in particular on hazard/agent, health outcomes, exposure assessment, target populations, risk characterisation, temporal character, scenarios or policy questions analysed, analysis of uncertainties, and interpretation and presentation of the assessment results. Detailed review of the studies allowed us to evaluate the strengths and shortcomings of methods typically used, and to make recommendations on how assessment of population health impacts of exposure to DBPs might be improved.

3. Results and discussion

In total, we identified 40 population health impact assessment studies that met our eligibility criteria for inclusion in this review (Table 1).

3.1. Populations

The populations defined in the majority of studies were those of individual countries, regions, cities or those served by individual waterworks or distribution systems. Eight studies were done in Canada, 8 in the USA, 5 in Turkey, 3 in China (one jointly reported with a Canadian study), 2 in Korea, 2 in Pakistan, 2 in Taiwan, and one each in Brazil, Germany, Hong Kong, India, Italy, Japan, Lebanon, Mexico, the Netherlands and New Zealand. Hypothetical populations were defined in 2 studies (Black et al., 1996; Havelaar et al., 2000), and one laboratory-based study focused on 6 subjects exposed to DBPs under experimental conditions (Jo et al., 1990). In one study, sensitive population subgroups were identified, comprising women of reproductive age and developing foetuses (USEPA, 2005). Surveyed demographic characteristics pertaining to these populations (in terms of sex- or age-structure) were taken into account in few assessments, and commonly existing general point estimates or distributions of body weight, water consumption rates, inhalation rates etc. were used when characterising exposures. In some cases not taking into account the demographic structure or behavioural characteristics of populations may result in a misclassification of the risk status of certain population strata. For example, bladder cancer has been found to be associated with DBPs only in males, and incident cases occur extremely infrequently in those below the age of 40 years. Estimation of numbers of cases attributable to exposure to DBPs should be made with adequate consideration of both age and sex stratification of the target population.

3.2. Hazard/agent

Twenty-four studies investigated solely THM4, 8 studies focused only on trichloromethane (TCM), and 5 studies looked at THM4 and some HAAs. One study focused on TCM, bromodichloromethane (BDCM) and dibromochloromethane (DBCM) only. One study looked at ingestion of bromate, which is produced due to disinfection with ozone, and one used residence in a zone where drinking water was chlorinated as an indicator of DBP exposure. Only one study explicitly considered contamination of drinking water by pathogens (specifically *Cryptosporidium parvum*), in spite of the very clear policy need for assessments in which cancer risks associated with DBPs are balanced with the benefits of disinfection (Havelaar et al., 2000).

3.3. Health outcomes

Almost all studies focused on the risk of cancer, with the vast majority of studies estimating LECR rather than risks of specific cancers. This method requires the use of PFs that are derived from the most sensitive tumour endpoint in a set of animal studies. Although theoretically this is protective against other cancers, it cannot be assumed that this same endpoint would be that occurring in humans. As such, the degree to which the LECR calculated provides an upper bound estimate of risk of *any* cancer is unknown. Five studies looked at specific cancers: bladder cancer (Attias et al., 1995; Malcolm et al., 1999; USEPA, 2005), colorectal cancer (Malcolm et al., 1999; USEPA, 2005), and renal cell cancer (Havelaar et al., 2000). Generic non-carcinogenic risks were estimated in 14 studies, quantified using hazard quotients (or hazard indices). Specific non-cancer outcomes included microbial infections (Havelaar et al., 2000), foetal loss (USEPA, 2005), and birth defects (Malcolm et al., 1999).

Metrics such as LECR and HI are not particularly informative in population health impact assessment. Upper bound estimates of LECR

Table 1
Summary of health risk and impact assessments of drinking water disinfection by-products.

Reference	Issue framing					Exposure assessment		Exposure-/dose-response	Risk characterisation	Analysis of uncertainty	Outcome metric
	Target population	Hazard/ agent	Health outcome	Temporal framing	Scenario(s) considered	Exposure route	Exposure assessment method				
(Lahey & Connor 1983)	Population of Nassau County, Long Island, USA	Chlorinated chemicals including TCM – unclear if TCM is as DBP or other source in ground water	Cancer (unspecified)	Not specified	Disposal of chemical waste on land and at sea	Ingestion of DW (and ingestion of fish)	Doses estimated by assuming 2 l/day (and 6.5g fish/ day) No details of levels of TCM in water presented	Upper bound PF (source of data not presented)	LECR estimated as product of potency by estimated dose (few details provided) Sum of risks for each chlorinated chemical	N/a	LECR for entire population due to ingestion of TCM
(Jo et al. 1990)	Six subjects in an experimental study, New Jersey, USA	TCM	Cancer (unspecified)	Water samples taken prior to showering – risks estimated over a lifetime	Comparison between risks associated with drinking or showering in the same DW	Multipathway (ingestion of DW, dermal contact and inhalation via showering)	Tap water sampled after each of 13 showers Shower dose: breath analysis for TCM pre- and post-showering	Upper bound PF derived from linearised model of single ingestion animal study Ingestion PF applied to all exposure routes	Doses were established with deterministic models, using general population exposure parameters LECR calculated from dose and PF	N/a	LECC due to dose of TCM in a theoretical population of one million
(Attias et al. 1995)	Five regions of Sardinia, Italy	THM4	Cancer (unspecified) using toxicological data, and bladder cancer using epidemiologic data	THM4 levels assumed to be constant over previous 2 decades. Baseline rates of bladder cancer averaged over 2 decades (latency)	Comparison of estimations of response using toxicological and epidemiologic methods	Ingestion of DW	Household DW monitoring data	PFs estimated from toxicological data using both multistage and linearised multistage models Epidemiologic risk estimates adapted from a meta-analysis on bladder cancer (Morris et al. 1992)	For animal data: unit risks From human data: unit lifetime risk expressed as incremental lifetime carcinogenic risk (derived from average relative risk model, incorporating baseline rates of bladder cancer)	Analysis of uncertainties introduced due to using different data and methods (toxicological/ epidemiological) plus presentation of risk estimates based on MLE PF (in addition to upper bounds)	Unit risks (incremental lifetime carcinogenic risk per µg/l of THM) expressed as the probability of tumour induction
(Black et al. 1996)	Hypothetical population served by a typical surface water DWTP in the USA	THM4 and 2 HAAs (no risk analysis presented for HAAs)	Cancer (unspecified)	Simulated exposure annual risk calculated	Investigation of the effects on health risks under a number of scenarios relating to implementation of organic carbon removal technologies	Ingestion of DW	Exposure entirely simulated: formation of THM4 at the DWTP due to treatment of typical US surface water was modelled using a number of predictive models	Published upper bound $PF_{ingestion}$	Risk estimates calculated as product of PFs and modelled exposures	Sensitivity analysis of parameters in treatment technologies An extensive list of modelling assumptions is provided	Annual cases of cancer attributable to exposures in a theoretical population of one million
(Chung et al. 1997)	Six major river systems and their distribution systems across the Republic of Korea	THMs (as part of a suite of 80 contaminants including VOCs, PAHs, pesticides, metals)	Cancer (unspecified)	Two years (1993-1995) of exposure estimates extrapolated over lifetime	Comparison of risks (calculated against an implicit zero risk baseline) for each contaminant as means of prioritising DW monitoring	Multipathway (ingestion of DW, dermal contact and inhalation via showering)	LADE estimated using PDFs of body weight and consumption, based on sampling of raw, treated and tap water in 6 cities	Upper bound PFs (published and derived from animal data)	For carcinogens: LADE multiplied by upper 95% CI on PFs derived using multistage model (No THMs were considered as non-carcinogens)	MCS (exposure)	Lifetime excess cancer risks attributable to exposure to THMs
(Malcolm et al. 1999)	New Zealand	Chlorination DBPs	Cancers of the bladder, rectum and colon; birth defects	Annual	Disinfection vs baseline scenario of no disinfection (chemical risk factors only)	Ingestion of DW (not specified)	Rough approximations of ever-never exposure to chlorinated water	Relative risk from epidemiological study	PAR% for all health outcomes; then applied to cancer and birth defect registry data	N/a	Annual cases of bladder, rectum and colon cancer, and cases of birth defects, attributable to exposure to DBPs
(Havelaar et al. 2000)	Hypothetical population served by an ozonating DWTP in the Netherlands (including immune-compromised subgroup)	Bromate (ozonation DBP)	Renal cell cancer and infections with *Cryptosporidium Parvum*	Annual averages of raw water data used – can be considered as valid for a typical plant operating over one year at the time of study publication	Comparison of the risks of disinfection (chemical) with its benefits (microbial) by way of explicit scenarios relating to use of ozonation and an immune-compromised population subgroup	Ingestion of DW	Predictive models used to generate estimates of bromate and microbial contamination at DWTP Daily ingested dose derived from concentration multiplied by typical daily ingestion	Both maximum likelihood estimate (MLE) and probabilistic estimate of dose-response for renal cell cancer based on animal data fitted with linearised multistage model	MLE of lifetime excess risk derived from the animal model used to predict renal cell cancer incidence at given level of exposure DALYs then calculated as per standard methods using life expectancies, duration of disease states and severity weightings	MCS to account for variation in exposure and response parameters for renal cell cancer Additional animal data fitted in model to explore heterogeneities Univariate sensitivity analysis used to investigate change in model input variables	DALYs per million person years

Table 1 (*continued*)

Reference	Issue framing					Exposure assessment		Exposure-/dose-response	Risk characterisation	Analysis of uncertainty	Outcome metric
	Target population	Hazard/agent	Health outcome	Temporal framing	Scenario(s) considered	Exposure route	Exposure assessment method				
(Hsu et al. 2001)	Three areas in different regions of Taiwan supplied by 3 DWTPs	THM4	Cancer (unspecified)	Water samples taken regularly over period 1994-1997 Maximum of 30 years of exposure assumed, but lifetime cancer risk calculated	Implicit baseline of zero exposure to THMs	Ingestion of DW	Geometric means of THM concentrations (monitoring data at DWTPs) Age-adjusted exposure calculated from generic assumptions on body weight, consumption rates etc.	Published upper bound $PF_{ingestion}$	Exposure multiplied by published PFs Rapid appraisal and prioritisation method applied after (R. L. Smith 1996)	N/a	LECR due to individual and total THMs
(Sadiq et al. 2002)	Two neighbouring towns in Newfoundland, Canada	TCM	Cancer (unspecified)	Two periods in 1998 (summer and winter); exposure estimates extrapolated over lifetime	DWTP with and without GAC	Ingestion (simulated with PDFs of generic population physical parameters)	Sampling survey throughout a DW distribution network Bootstrapping used to infer robust non-parametric PDFs from these data	Published upper bound $PF_{ingestion}$	Chronic daily ingestion multiplied by PF	Bootstrapping (exposure assessment) MCS (exposure assessment and risk characterisation)	LECR due to ingested TCM
(Williams et al. 2002)	California, USA	TCM (as one of 6 VOCs) in DW and raw water (from groundwater sources)	Cancer (unspecified)	1995-2001	Comparison of cancer risks adjusted for detection frequency of the VOCs with unadjusted	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	State wide sampling survey of ~2500 DW systems (mean detected concentrations)	Published upper bound PFs	Potential LCR calculated as LADD multiplied by PF	N/a	Relative lifetime cancer risk
(Fehr et al. 2003)	Population of North Rhine-Westphalia, Germany	TCM (as one of 8 carcinogenic chemical contaminants in water)	Cancer (unspecified)	Not specified, but exposure in baseline scenario based on 'current' monitoring data; exposure estimates extrapolated over lifetime	Comparison of 2 water privatisation policies: business-as-usual (public water supply) vs. privatised water supply	Ingestion of DW (CDI calculated using PDFs for body weight and water intake)	Baseline scenario exposure based on current levels of contaminants. Privatisation scenario contaminant levels based on percentage exhaustion of regulatory limits	Published upper bound $PF_{ingestion}$, specified as a) a point estimate and b) a PDF Values of $PF_{ingestion}$ not provided	Deterministic and probabilistic estimation of risk by multiplying PFs by exposure distributions Unit risks for all carcinogens were summed and multiplied by the entire population	MCS (exposure assessment) Sensitivity analysis based on deterministic and probabilistic methods in assessment of exposure and definitions of PFs	LECC due to increase in carcinogens (including ingestion of TCM)
(Sofuoglu et al. 2003)	Two populations in Arizona, USA	TCM (as one of a suite of contaminants, including metals, volatile organic compounds (VOCs) and pesticides	Cancer (unspecified)	NHEXAS data from 1998	Implicit baseline of zero exposure to THMs Comparison between 2 areas with different hypothesized difference in environmental quality	Ingestion of DW	NHEXAS Arizona sampling study (DW from households) Annual daily ingestion estimated using probabilistic simulation	Published upper bound $PF_{ingestion}$ Values not provided	Product of PF and annual daily exposure	Bootstrapping and MCS (exposure assessment)	LECR due to ingestion of TCM
(Lee et al. 2004)	19 districts of Hong Kong	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	Temporal frame of sampling survey not presented; annual excess cases of cancer	Implicit baseline of zero exposure to THMs	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Measured THM4 across DW distribution network CDIs calculated using generic US population parameters	Published upper bound PFs RfDs for oral and dermal routes	Sum of exposure-route specific LECR calculated as chronic daily exposure multiplied by PFs for each THM after (Gratt 1996). HI calculated assuming risk additivity	N/a	Annual excess cases of cancer and HI due to multipathway exposure to THM4
(Tokmak et al. 2004)	Ankara, Turkey	THM4	Cancer (unspecified)	Temporal frame of sampling survey not presented; annual excess cases of cancer	Implicit baseline of zero exposure to THMs	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Samples of consumer tap water in 22 districts Estimation of exposure after Lee et al. (2004)	Upper bound PFs and RfDs from Lee et al. (2004)	Method after Lee et al. (2004)	N/a	Annual excess cases of cancer and HI due to multipathway exposure to THM4

(*continued on next page*)

Table 1 (*continued*)

Reference	Issue framing					Exposure assessment		Exposure-/dose-response	Risk characterisation	Analysis of uncertainty	Outcome metric
	Target population	Hazard/ agent	Health outcome	Temporal framing	Scenario(s) considered	Exposure route	Exposure assessment method				
(USEPA 2005)	Population of US potentially exposed to DBPs from drinking water (~263 million) Subgroup analyses carried out for women of child-bearing age and developing foetuses	TTHM and HAA5	Bladder cancer, colon cancer, adverse birth outcomes (specifically foetal losses)	Temporal variability accounted for in exposure models "Cessation lag" function used to project bladder cancer cases avoided each year after implementation as a result of the Stage 2 DBPR over a 100-year period	Four alternatives relating to regulatory requirements on drinking water providers (Stage 2 DBPR)	All routes (implicitly, as volatile and non-volatile DBPs considered and epidemiological data used for ERF)	Modelling of drinking water concentrations of DBPs, incorporating uncertainties relating to compliance, spatial and temporal variability	Epidemiological data from five studies (Toxicological data used for comparison only)	PAR, PAC (cases of cancer etc. avoided), dollars (LCR from toxicological data for comparison only)	Extensive uncertainty analysis: quantitative (MCS, sensitivity analysis, alternative models, populations, data etc.) and qualitative (lists of uncertainties and their potential effects)	Monetised costs and benefits
(Kavcar et al. 2006)	Izmir, Turkey	THM4 (as one group of several VOCs) in tap water and bottled water	Cancer (unspecified)	Not presented; lifetime cancer risk	Implicit baseline of zero exposure to THMs Comparison of tap water and bottled water	Ingestion of DW	Sampling survey of 100 households	Published upper bound $PF_{ingestion}$, RfD used instead of PF for TCM	Chronic daily ingested dose multiplied by PF RfD used to calculate HQ for TCM as secondary carcinogen	MCS (exposure assessment)	LECR due to ingestion of THM4
(Nazir & Khan 2006)	Three communities in Newfoundland, Canada	TCM (as a "representative chemical" for the THM mixture)	Cancer (unspecified)	Summer and winter in one year; averaged over lifetime	Comparison of shower design parameters and shower usage	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Process-based modelling of inhalation and dermal contact during showering after Jo et al. (1990)	Published upper bound $PF_{inhalation}$ through inhalation Published oral RfD used instead of PF for ingestion and dermal	Modelled probabilistic exposure estimates multiplied by PF (or RfD) RfD used to calculate HQ for TCM as secondary carcinogen	MCS (exposure assessment) Two alternative models of shower air THM concentrations	LECR due to multi-pathway exposure to TCM
(Uyak 2006)	Istanbul, Turkey	THM4	Cancer (unspecified) and non-cancer outcomes (unspecific)	24-week sampling survey (summer, 2004); averaged over lifetime	Implicit baseline of zero exposure to THMs	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Sampling of household tap water Exposure assessed after Lee et al. (2004)	Published upper bound PFs (including rescinded data for TCM) and RfDs	Method after (S. C. Lee et al. 2004) Excess cases calculated as lifetime cancer risk multiplied by Istanbul population	N/a	Annual excess cases of cancer and HI due to multipathway exposure to THM4
(Aslan & Turkman 2007)	Izmir, Turkey	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	One-year survey; averaged over lifetime	Implicit baseline of zero exposure to THMs	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Water samples at DWTP Exposure assessed after (S. C. Lee et al. 2004)	Published upper bound PFs (including rescinded data for TCM)	Method after (S. C. Lee et al. 2004)	N/a	LECR and HI due to multipathway exposure to TCM
(Navarro et al. 2007)	Four communities in central Mexico	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	2-week sampling program in May 2005	Implicit baseline of zero exposure to THMs	Ingestion of DW	Sampling of household tap water	Published upper bound PFs for brominated THMs. RfD used for TCM	Chronic daily ingestion multiplied by PFs (bromide THMs) RfD used to calculate HQ for TCM as secondary carcinogen	MCS (exposure)	LECR due to ingestion of THM4
(Semerjian & Dennis 2007)	Lebanon	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	One year sampling survey (spring, summer, winter)	Implicit baseline of zero exposure to THMs	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Water samples "collected randomly from various water sources and water distribution systems" LADDs were then calculated, according to Lee et al. (2004)	Published upper bound PFs (including rescinded data for TCM)	Two approaches used: (1) WHO index for additive toxicity; and (2) USEPA-approved Risk Assistant model	Sensitivity analysis of 2 methods of risk characterisation	LECR and HI due to multipathway exposure to THM4

Table 1 (*continued*)

Reference	Issue framing					Exposure assessment		Exposure-/dose-response	Risk characterisation	Analysis of uncertainty	Outcome metric
	Target population	Hazard/ agent	Health outcome	Temporal framing	Scenario(s) considered	Exposure route	Exposure assessment method				
(G. S. Wang et al. 2007)	Three metropolitan districts of Taiwan, and one island county (Kinmen)	THM4	Cancer (unspecified)	One year of sampling between July 2002 and May 2003	Implicit baseline of zero exposure to THMs	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Water samples at DWTP Exposure assessed after Lee et al. (2004), using updated showering models, and using PDFs for some parameters	Published upper bound PFs (including rescinded data for TCM)	Method after (S. C. Lee et al. 2004)	MCS (exposure) Sensitivity analysis on effect of using PFs in exposure pathways for which they were not specifically intended	LECR due to multipathway exposure to THM4
(W. Wang et al. 2007)	Fifteen waterworks in Beijing, China and three DWTPs in Canada	THM4 and haloacetic acids	Cancer (unspecified) and non-cancer outcomes (unspecified)	China: one-off sampling survey Canada: averages of monthly measurements over 1 year	Implicit baseline of zero exposure to THMs Comparison of risks in 2 countries Comparison of risks under three types of treatment in Canada	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Water samples at DWTP Exposure assessed after Lee et al. (2004)	Published upper bound PFs (including rescinded data for TCM)	Method after (S. C. Lee et al. 2004) Excess cases calculated as hazard index multiplied by appropriate populations	A list of sources of uncertainty was presented, in particular recognising that estimates are upper bound	LECR and HI due to multipathway exposure to THM4
(Baytak et al. 2008)	Izmir, Turkey	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	Sampling survey carried out between July 2006 and April 2007	Implicit baseline of zero exposure to THMs	Ingestion of DW	Tap water samples taken across five districts of Izmir Exposure assessed after Lee et al. (2004), with body weight and water consumption represented probabilistically	Published upper bound PFs Oral RfD used for TCM	Method after (S. C. Lee et al. 2004) RfD used to calculate HQ for TCM as secondary carcinogen	MCS (exposure)	Probabilistic estimates of LECR and HI due to multipathway exposure to THM4
(Viana et al. 2009)	Ten metropolitan districts of Fortaleza, Brazil	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	Sampling survey carried out between October and December 2004	Implicit baseline of zero exposure to THMs	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Sampling of household tap water Exposure assessed after Lee et al. (2004)	Published upper bound PFs and RfDs No values presented	Method after (S. C. Lee et al. 2004)	N/a	LECR and HI due to multipathway exposure to THM4
(Chowdhury & Champagne 2009)	Three major cities in Ontario, Canada	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	2000-2004; annual cancer risk estimated	Variable shower stall volumes and durations Implicit baseline of zero exposure to THMs	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Sampling of household tap water Process-based modelling of inhalation and dermal contact during showering	Published upper bound PFs and RfDs Oral RfD used for TCM	Adaptation of method after (S. C. Lee et al. 2004) RfD used to calculate HQ for TCM as secondary carcinogen	MCS (exposure assessment)	PDFs of LECR, annual excess cases of cancer and HI due to exposure to THM4 via showering
(Buteau & Valcke 2010)	Province of Quebec, Canada (adult population, and 2 presumed susceptible subgroups: toddlers; infants)	TCM (as surrogate for THM4)	Non-cancer outcomes (unspecified)	Quarter of year where exceedances of guideline were more frequent and THM levels highest (July-October).	Two explicit exposure scenarios defined over high THM quarter: (1) average [TTHM]; (2) average of all [TTHM] >80μg/L	Multipathway (ingestion of DW [infants consuming 100% formula mixed with DW], and inhalation and dermal contact via showering [bathing for infants & toddlers]	Distributions fit to monitoring data of TCM concentrations at tap. Absorbed doses calculated for ingestion, and for inhalation and dermal contact during showering using process-based model	Intermediate MRLs used as TRVs to account for short exposure period. MRLs based on number of animal studies (liver enzyme activity) and occupational studies (hepatitis)	Method after (USEPA 2004), whereby RQ was calculated for each exposure pathway, which were summed (since all related to hepatic effects)	MCS (exposure assessment) PDFs of some exposure variables and population characteristics Sensitivity analysis for each input variable	Firstly, estimation of non-carcinogenic risk (RQ), then back calculated to provide DW concentration that should not be exceeded to maintain RQ <1
(Chowdhury & Hall 2010) ***RETRACTED***	20 most populated cities in Canada	THM4	Cancer (unspecified)	Seasonal averages for 2002-2008 applied to lifetime	None	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Distributions fit to DW monitoring data obtained from regulatory and other published sources	Published upper bound PFs Oral RfD used for TCM	Method after (S. C. Lee et al. 2004) RfD used to calculate HQ for TCM as secondary carcinogen	MCS (exposure assessment) PDFs of monitoring data – other exposure variables and population characteristics deterministic	LECR and annual excess cases of cancer due to multipathway exposure to THM4

(*continued on next page*)

Table 1 (*continued*)

Reference	Issue framing					Exposure assessment		Exposure-/dose-response	Risk characterisation	Analysis of uncertainty	Outcome metric
	Target population	Hazard/ agent	Health outcome	Temporal framing	Scenario(s) considered	Exposure route	Exposure assessment method				
(LaKind et al. 2010)	NHANES blood data (considered broadly representative for US population)	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	1999-2004	None	Blood levels of THM from all exposure routes	Biomonitoring equivalents (BE) calculated from levels of THMs in ~2,500 NHANES blood samples	THM-specific BEs derived from blood concentrations using pharmaco-kinetic human and animal data. TCM not include as PF withdrawn by USEPA.	Blood THM concentrations compared with BEs, and each THM assigned low, medium or high priority for follow-up	95% CIs on blood concentrations propagated	Priorities for risk assessment follow-up based on LECR. Hazard index for non-cancer outcomes.
(Basu et al. 2011)	10 DWTPs in 2 states (Jharkand and West Bengal), India	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	March 2009 to June 2009; applied to lifetime	Worst case scenario assumed – most distal points in distribution system sampled, in summer months	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	44 triplicate tap water samples were collected at DWTP endpoints and analyzed from 11 locations	Published upper bound PFs (including rescinded data for TCM)	Method after (S. C. Lee et al. 2004)	Sensitivity analysis carried out for some exposure variables (exact methods are unclear)	LECR and HI due to multipathway exposure to THM4
(Chowdhury et al. 2011) *In italics: updates according to Chowdhury (2012) response to commentary (Bull et al. 2012)*	Canada (all provinces)	THM4	Cancer (unspecified) – medical costs calculated assuming cases of bladder and colorectal cancer	1993 to 2007, depending on province; applied to lifetime (70 yrs)	None	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Quarterly monitoring data of DW from household taps collected from provincial offices and Health Canada reports. Age-adjusted intake rates used.	Published upper bound PFs (including rescinded data for TCM) *Upper bound PFs for BDCM, DBCM and TBM only*	Method after (S. C. Lee et al. 2004)	MCS – 10^{th}, 50^{th} and 90^{th} percentiles of some exposure variables used to fit triangular distributions.	LECR and annual excess cases of cancer, and healthcare costs due to multipathway exposure to THM4
(Legay et al. 2011)	Nine distributions systems in 2 regions of Quebec, Canada	THM4 and DCAA	Cancer (unspecified)	2006-2008; applied to lifetime	Cancer risk assessment considering chloroform as a carcinogen versus chloroform as a non-carcinogen	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	PDFs fit to monthly sample survey data based on DW sampling from taps at 46 sites (one per zone) in 9 distribution systems	Published upper bound PFs (including rescinded data on TCM) Separate analysis carried out not including TCM	Method after (S. C. Lee et al. 2004) with some adaptations for showering model	MCS (exposure assessment) PDFs of some exposure variables and population characteristics	LECR due to multipathway exposure to THM4 and DCAA
(Liu et al. 2011)	One DWTP in Shanghai, China	THM4	Cancer (unspecified)	2009; applied to lifetime	Seasonal variations (spring, summer, autumn, winter)	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	24 samples taken at DWTP prior to distribution	Published upper bound PFs (including rescinded data for TCM)	Method after (S. C. Lee et al. 2004)	None	LECR due to multipathway exposure to THM4 and DCAA
(Pardakhti et al. 2011)	Seven water districts in Tehran, Iran	THM4	Cancer (unspecified)	March-September 2009; applied to lifetime	None	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	63 samples of household tap water taken from 21 sampling locations (3 replicate samples at each at one time point)	Published upper bound PFs (including rescinded data for TCM) and RfDs	Method after (S. C. Lee et al. 2004)	None	LECR and annual excess cases of cancer due to multipathway exposure to THM4
(Yamamoto 2011)	Three water utilities serving Osaka City, Japan	THM4	Cancer (unspecified) and non-cancer outcomes (unspecified)	Summers 1998-2004, before and after installation of advanced treatment	Comparison of conventionally treated water and advanced treated water (ozonation step)	Only ingestion route was considered	5 sampling campaigns of household tap water at (48 measurements taken at 31 locations)	Published upper bound $PF_{ingestion}$ (including rescinded data for TCM)	Based on USEPA methods for calculating lifetime cancer risk for ingestion	Risks estimated at mean and minima and maxima of exposure measurements.	LECR, annual excess cases of cancer and HI due to multipathway exposure to THM4
(Venkataraman & Uddameri 2012)	48 counties in coastal Texas, USA, underlain by Gulf Coast aquifer	THM4 used for showering	Cancer (unspecified)	2004-2008; applied to lifetime	Inhalation risks of (a) first person to use the shower in the day; and (b) subsequent shower user	Multipathway (details on inhalation via showering; no details on ingestion or dermal routes)	Predictive model of THM formation in GW using kriging; validated against survey data of THM4 for 2004-2008. Surface water THM4 data from monitoring survey	Published upper bound $PF_{ingestion}$ Oral RfD used for TCM	Based on USEPA methods for calculating lifetime cancer risk for inhalation (no details provided for ingestion pathway) RfD used to calculate HQ for TCM as secondary carcinogen	None	LECR, and HI due to exposure to THM4 via showering

Table 1 (*continued*)

Reference	Issue framing					Exposure assessment		Exposure-/dose-response	Risk characterisation	Analysis of uncertainty	Outcome metric
	Target population	Hazard/ agent	Health outcome	Temporal framing	Scenario(s) considered	Exposure route	Exposure assessment method				
(Amjad et al. 2013)	Two cities in Pakistan—Rawalpindi and Islamabad	TCM, BDCM & DBCM	Cancer (unspecified) and non-cancer outcomes (unspecified)	Not presented	None	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Sampling of tap water at 20 locations	Published upper bound PFs (including rescinded data for TCM) and RfDs	Method after (S. C. Lee et al. 2004)	None	LECR, and HI due to multipathway exposure to TCM, BDCM and DBCM
(Gan et al. 2013)	Population served by 10 water treatment plants in three Chinese cities — Guangzhou, Foshan and Zhuhai	THM4 and 2 HAAs (DCAA & TCAA)	Cancer (unspecified)	July and December 2011, January and November 2012; applied to lifetime	None	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Sampling survey of tap water, with calculation of ingestion (drinking only), inhalation and dermal contact (shower stall model) based on mean individual THM concentrations.	Published upper bound PFs (including rescinded data for TCM)	Method after (S. C. Lee et al. 2004)	None	LECR due to multipathway exposure to THM4 and 2 HAAs
(Lee et al. 2013)	Adult population served by 6 water treatment plants in Seoul, Korea	THM4	Cancer (unspecified)	2009; applied to lifetime	Comparison of boiled water with unboiled water for ingestion pathway	Multipathway (ingestion of DW, dermal contact and inhalation of DBPs via showering)	Distributions fit to monitoring data of TCM concentrations in DW at tap. Absorbed doses calculated for ingestion, and for inhalation and dermal contact during showering using process-based model	Published upper bound PFs (including rescinded data for TCM)	Adaptation of method after (S. C. Lee et al. 2004)	MCS (exposure assessment) Sensitivity analysis on some exposure parameters	LECR due to multipathway exposure to THM4
(Karim et al. 2013)	Population of 15 towns in Karachi, Pakistan	THM4	Cancer (unspecified) and non-cancer (unspecified)	March 2010; applied to lifetime	N/a	Ingestion and dermal absorption	DW samples from 30 locations, interpolation by kriging across entire study area.	Published upper bound $PF_{ingestion}$ and RfD No values presented	Adaptation of method after (S. C. Lee et al. 2004)	None	LECR and HI due to multipathway exposure to THM4

Key: CDI chronic daily intake; DALY disability-adjusted life year; DWTP drinking water (DW) treatment plant; GAC granulated activated carbon; LADE lifetime average daily exposure; LECC lifetime excess cases of cancer; MCS Monte Carlo simulation; MLE maximum likelihood estimate; MRL minimal risk level; PAH poly aromatic hydrocarbons; PAR% population attributable risk percent; PDF probability distribution function; PF potency factor; RQ risk quotient; TRV Toxicological reference values; VOC volatile organic compound

provide no information regarding the implications of the burden of cancer on society in terms of type, severity, survival times, population subgroups affected, associated effects on quality of life or costs to healthcare providers. Also, they do not provide useful information on potential health benefits that might be associated with policies or interventions that might alter exposures, either deliberately or as an unintended consequence. Use of data and methods that allow estimation of the burden of specific health outcomes would result in more useful information to a range of decision-makers, as was done in those studies that derived exposure–response data from epidemiological studies. In the Havelaar et al. (2000) study, the maximum likelihood estimate of risk of a specific cancer outcome (renal cell cancer) derived from animal data was explicitly assumed to correspond to the same outcome in humans, and the implications to public health estimated in terms of the severity and duration of that outcome. In one assessment, estimates of LECR were monetised using cost models for bladder and colorectal cancers (Chowdhury et al., 2011), although it later transpired that the methods used in this paper were wrong (Bull et al., 2012). Revised estimates were subsequently published, indicating that the original LECR was considerably overestimated (Chowdhury, 2012). When correctly applied, such an approach might seem to be an improvement over estimates of LECR-based lifetime cancer cases, although the generic nature of LECR limits its validity and we would recommend the more appropriate use of epidemiological data in deriving estimates of attributable cases of a specific cancer outcome. Although epidemiological data on specific health outcomes were used in the USEPA (2005) assessment, estimates of lifetime cancer risk based on slope factors were presented for the purposes of comparison. Notably, these were presented alongside appropriate caveats regarding the limitations associated with use and interpretation of such data.

3.4. Exposure assessment

Apart from the laboratory-based, experimental study reviewed (Jo et al., 1990) and study of biomarkers of exposure (LaKind et al., 2010), all studies employed one of three types of exposure assessment: (1) ecological assessments, where populations were assigned exposure levels based on measured or modelled concentrations of DBPs in drinking water; (2) individual level assessment, where a survey of measurements was undertaken for each subject; or (3) binary ecological assessment, where the population was divided according to water supply chlorination status in their area of residence. The first of these methods was used most frequently, with DBP concentrations in drinking water supplies being derived from sampling surveys or monitoring data. In some cases, however, DBP concentrations were entirely based on models, using typical source water quality and treatment procedures as input variables (Black et al., 1996; Havelaar et al., 2000), or on complex semi-empirical models developed using monitoring data and treatment plant characteristics (USEPA, 2005).

Given concentrations of DBPs in drinking water, exposure was calculated either solely for the ingestion pathway, or via multiple pathways. Several process-based models were used to calculate the concentrations of DBPs taken into the body. This multipathway approach is based on various USEPA regulatory risk assessment guidelines (USEPA, 1986, 1999, 2002b) and was introduced into the field of assessing population health impact of DBPs by Lee et al. (2004); many of the subsequent

studies reviewed used the Lee et al. (2004) study as a template for this kind of assessment.

In those studies where ingestion was considered as the sole pathway of exposure, those pathways in which volatility of DBPs plays an important role were ignored. While this is not necessarily a problem for non-volatile components of the DBP mixture, it is a serious problem for THMs, since net exposure may in fact be dominated by inhalation during bathing or showering (Nieuwenhuijsen et al., 2000b; Richardson, 2005). In some studies, TCM was used as an indicator for THM4. We would strongly recommend against such an approach: differences in volatilities of individual THMs, in correlations between TCM and the other THMs throughout the distribution network, and in the likely modes of toxicity of individual THMs are all likely to bias risk prediction estimates.

Duration of sampling surveys or periods of monitoring data varied between 2 weeks (Navarro et al., 2007) and 6 years (Williams et al., 2002). In some cases, no information was given regarding the timing or duration of sampling surveys (e.g. Amjad et al. (2013)), which makes the results impossible to interpret. Variations in past exposure were typically ignored. Extrapolation of current levels through time may or may not be valid depending on the temporal stability of contaminant levels in the drinking water sources, methods and technologies employed at treatment plants, and characteristics of the distribution network. When risks based on short term or point estimates of exposure are applied to a population in calculating LECR, for example, those exposure estimates are considered valid averages for 70 years. It has been shown, however, that there is a considerable degree of variability in THM concentrations both within and between 24-hour samples (e.g. Smith et al., 1980; Rodriguez and Serodes, 2001), on a seasonal basis (e.g. Parvez et al., 2011), and among year-on-year averages (e.g. Toledano et al., 2005). Usage habits of water might also be expected to change considerably in time: e.g. tap water consumption to bottled water, bathing to showering, hand washing of clothes and dishes to automatic washing. Calculating health impacts without considering possible changes in exposure over time is particularly problematic for carcinogens, since the bladder cancers associated with exposure to DBPs in epidemiological studies are characterised by long latency times. The USEPA (2005) assessment explicitly incorporated such temporal components in modelling regulatory compliance related to implementing a new rule, and in modelling cessation lag (period between reduction in exposure to a carcinogen and that point when the full risk reduction benefit is realised by affected individuals).

In some studies, concentrations of DBPs at the DWTP were used as exposure estimates for the target population (e.g. Black et al., 1996). DBP concentrations are known to vary considerably within water distribution networks (Amy et al., 2000); levels of THMs have been found to increase with residence time, while other DBPs have been found to decrease (haloacetonitriles, haloketones, chloropicrin, and haloacetic acids) (Chen and Weisel, 1998). Ideally, concentrations of DBPs at the individual consumer taps would be used to characterise target population exposure. Where concentrations at the tap are not available for the entire target population (or are available only at a poor spatial resolution), relationships between concentrations of DBPs at the DWTP and at different points within the distribution network should be explored and quantified.

Geographical information systems (GIS) were used in two studies to produce risk maps based on spatial exposure data. Venkataraman and Uddameri (2012) used TTHM monitoring data and groundwater parameters from a very limited number of locations to model TTHM concentrations at those locations, and kriging was used to interpolate TTHM concentrations across a large area (some 30,000 miles^2). Karim et al. (2013) used kriging of data from a TTHM sampling survey (at 30 locations) to estimate TTHM concentrations for several million inhabitants. As DBP concentrations do not vary smoothly in space, but tend to vary heterogeneously and unpredictably according to the configuration of the network, we consider that neither approach would produce anything other than extremely unreliable exposure estimates for the target populations concerned.

In general, the effort invested in very detailed exposure models in support of an assessment that then uses regulatory tools such as PFs to estimate risk may not be rewarded in terms of proportional improvements in the risk assessment results. In such cases, we would propose that it would be more efficient—and useful from the point of view of informing public health policy—to invest more effort in better characterising the exposure–response functions used. Such risk assessment research should generally be geared towards optimising the use of limited risk management resources (Jardine et al., 2003). In the study by Lee et al. (2004), and several assessments using the same methodology (Tokmak et al., 2004; Viana et al., 2009; Wang et al., 2007a,b), the authors compare cancer risks according to individual trihalomethane species through single exposure pathways. For example, a very detailed process-based model of exposure during showering supports a risk assessment that presents very precise risk estimates under various shower cubicle construction scenarios (Chowdhury and Champagne, 2009). Given the potentially very large uncertainties in the upper bound PFs used to characterise these exposures as risks, quantification of such relationships between behaviour and cancer risk, or comparisons of risks associated with specific exposure routes, are ultimately wholly misleading and have very low utility to decision-makers.

Overall, population health impact assessment should aim to use exposure data that are as similar as possible with exposure as defined in the study (toxicological or epidemiological) from which exposure–response data are derived. This congruence should be sought in terms of exposure medium and routes of intake, and in the temporal and spatial characteristics of those data. In general, the use of animal studies to predict *accurately* risk in humans is limited because exposure media and routes of intake in animal studies seldom represent those experienced in the human population. For example, high doses of chloroform administered to rodents by gavage as a single daily bolus in corn oil have been associated with tumours, in contrast to administration via drinking water where carcinogenicity has not been demonstrated even at doses 1000 times higher than typical guideline levels (Butterworth and Bogdanffy, 1999; Coffin et al., 2000). However, assessment of exposure in epidemiological studies of DBPs also tends to be limited due to practical difficulties in adequately characterising the many long-term exposure-determining habits and environments of study subjects.

3.5. Exposure– and dose–response

The results of population health impact assessments are highly dependent on the data selected to quantify exposure– or dose–response. In many ways, these data are central to the whole assessment, since they dictate the hazard, the form of the exposure metric and the type of health outcome that can be incorporated in the assessment. Where authors do not pay sufficient notice to (a) the framework within which such information was intended to be used; or (b) the veracity and/or validity of this information (i.e. by independently checking the sources from which these data arise), they risk miscalculating their results and may misinterpret the actual risk to the target population.

The majority of studies used toxicological dose–response data (usually upper bound PFs for cancer and RfDs for systemic effects) to estimate risk according to regulatory risk assessment methods. Three studies used epidemiological data in estimating exposure–response functions (Attias et al., 1995; Malcolm et al., 1999; USEPA, 2005). In the Attias et al. (1995) study, epidemiological risk estimates were obtained from a meta-analysis for THM exposure and bladder cancer (Morris et al., 1992) where risk estimates were presented for binary exposure data. In the USEPA (2005) study, OR for binary exposure was derived from a meta-analysis (Villanueva et al., 2003) for bladder cancer. For the purposes of sensitivity analysis, risk estimates for binary exposure data derived from five epidemiological studies and an OR/

average TTHM slope from a pooled analysis (Villanueva et al., 2004) were also used. A similar approach was employed for colon and rectal cancer, and for foetal loss. Of the studies using toxicological data, upper bound PFs were most commonly used as they were available from large regulatory risk assessment databases, such as the USEPA IRIS. These upper bound PFs result from application of linearised multistage (LMS) model to animal data so as to extrapolate to effects in humans. Application of LMS in this way generates estimates of non-zero cancer potency even when that parameter is zero (Crump, 1984): as such, actual risk may be anywhere below the quoted upper bound PF and zero (Felter and Dourson, 1998). The USEPA has specifically employed this method in the regulatory context to set guidelines at which the excess risk of cancer is essentially too small to estimate, so that public health is protected. We can say that these upper bound PFs are characterised by "several hidden political components that should not be there, if we wish to claim that risk assessment is a scientific exercise" (Tuomisto, 2005). Those well-acquainted with regulatory risk assessment have never claimed that risks estimated using PFs are accurate, even when differences between animals and humans are disregarded (Hrudey, 2009; Rodricks, 2007). The implications of these political or risk-management decisions, while made explicit in the original literature accompanying the risk assessment (see, for example, Smith, 1996), appear to have been forgotten in many of the cancer risk assessments reviewed here, as it is clear that the use of upper bound PFs will greatly overestimate true cancer risk when applied in population health impact assessment. Some studies used maximum likelihood estimates of cancer potency based on modelling of animal data rather than upper bound estimates so as to reduce the potential for overestimating the risk (Havelaar et al., 2000), and employed probabilistic definitions of cancer potency (Fehr et al., 2003; Havelaar et al., 2000) which were propagated into final risk estimates.

Several studies applied PFs developed for exposure through one pathway of exposure to another (Table 2). For example, $PF_{ingestion}$ for a given THM was applied to the inhalation pathway where $PF_{inhalation}$ was not available, or for dermal absorption factors. The extrapolation of exposure-route-specific factors from one route to another has been described as "at best difficult and at worst invalid" (Bull et al., 1995). In another study (Black et al., 1996), we found that carcinogenic risks were overestimated for BDCM, as a $PF_{ingestion}$ was not available and the PF for DBCM was used instead. Since risks are ultimately summed across pathways and DBPs in this approach to risk assessment, use of inappropriate PFs where specific data are not available necessarily overestimates risk.

All evidence used in an assessment should be valid at the time the assessment is carried out. The contents of online databases such as USEPA IRIS are continually subject to update as new evidence is reviewed. Understanding the validity of data and recognising which data should be used in an assessment are key tasks for the risk assessor. In some of the studies reviewed, outdated PFs were used without justification or explanation (Table 2), a fact that effectively invalidates these results. For example, although TCM was previously considered a genotoxic non-threshold carcinogen, its status has changed considerably in the past two decades as scientific understanding changed, to the extent that employing a PF for TCM after 2001 was not supported by scientific evidence. In 1994, in the absence of better information on the mechanism of its carcinogenicity, the USEPA applied default assumptions of low-dose linearity to TCM, and proposed setting a maximum contaminant level goal (MCLG) of zero. PFs were thus developed for TCM which incorporated this presumptive default, in support of the USEPA's belief that there was no safe level of exposure for chloroform (Pontius, 2003). In 1998, a review of new animal data was carried out which suggested that the available evidence pointed now towards TCM being a threshold carcinogen. Although the MLCG for TCM was not initially revised, an ensuing legal petition resulted in USEPA rescinding its zero MCLG and recommending the use of the RfD in lieu of $PF_{ingestion}$. Cancer effects related to TCM were then thought to be caused by a nongenotoxic cytotoxic mode of action (Butterworth and Bogdanffy, 1999) where hepatotoxicity was a prerequisite for carcinogenesis to occur (King, 2010; USEPA, 2002b). The USEPA IRIS assessment of the cancer risk of TCM formally noted as early as 2001 that the PF had been rescinded because the RfD—based on assessment of liver toxicity—was protective for cancer. All of those studies using a PF for TCM cancer risk after 2001 were carelessly erroneous. The fact that this was done by so many studies would suggest that the reason why a PF should not be used for TCM in cancer risk assessment is widely misunderstood. Risk assessments using linear assumptions about dose–response of this chemical would grossly overestimate actual risk in human populations (Butterworth, 2005). Although several studies used the RfD of 0.01 in place of the $PF_{ingestion}$ for TCM by the mid-2000s, many authors used the rescinded PFs several years later, even in studies published up to the present day (Fig. 1). Importantly, we noted that this issue of using outdated PFs is not limited to chloroform, but also applies to other THMs. For example, at the time of writing, PF values for BDCM were still available on the IRIS database that will probably be revised in the light of recent toxicological evidence (NTP, 2005), as was done by Health Canada in 2009. As such, we would recommend that authors making any use of data available from sources such as the USEPA IRIS database should check that the online information is truly representative not only of the Agency's actual position, but also of the best current scientific evidence. Publishing studies that neglect to use correct, up-to-date TCM data as issued by the USEPA ultimately undermines the validity of the risk assessment paradigm and may lead to unnecessary public alarm.

The studies that used epidemiological data generally made use of the best human-based information available at the time of their publication. Large, well-conducted epidemiological studies, and meta-analyses and pooled analyses of such data, are an alternative source of data from which exposure–response functions (ERF) can be derived, particularly where there is mechanistic information to support causal interpretation of the reported associations. In the case of epidemiological studies of DBPs and bladder cancer, the importance of recognising the lack of a causal mechanism cannot be overstated. Whereas ERF based on toxicological data can be used to estimate risk of (non-specific) cancer, using data from epidemiological studies allows the estimation of attributable risk of specific health outcomes in the target population, so long as the results are presented alongside a clear description of how well scientific evidence supports causality. Where several studies—or several pooled or meta-analyses—exist, sensitivity analysis should be carried out to quantify the potential impacts of their use on assessment results.

Interpretation of the results of epidemiological studies on DBPs and cancer—and their use in risk assessments—requires an understanding and acceptance of the various uncertainties that influence them. Measurement error in exposure assessment is a major concern, particularly since retrospective estimation of long-term exposure is difficult in the absence of reliable monitoring data. Since almost all studies have used a case–control design in order to be powerful enough to detect modest effects, there is a potential for recall bias. Several of these studies may also be subject to bias due to the use of hospital-based controls, where selection of diseases may not be accurate. In addition, the inaccuracies present in exposure estimates in these studies are indeed limited by non-systematic biases that may lead to reduction in precision of risk estimates, but the lack of specificity in the exposure metrics used also confers some advantage when ERFs derived from those studies are applied in population health impact assessment. Since the putative agents among the >600 DBPs in water have not been identified, existing epidemiological studies have tended to employ relatively simple proxies of exposure, which may be prone to misclassification of true exposure. This is evidently a weakness of existing epidemiological studies, but concentrations of THMs in the drinking water have nonetheless served as markers for unknown putative agents, and consistency in the risk estimates for bladder cancer may demonstrate that use of such a surrogate is in some way indicative of true exposure, and foregoes the need fully

Table 2
Summary of dose/exposure–response functions employed.

Name of study	PFs/SFs/RfDs (pathway, value, citation)
Lahey and Connor (1983)	TCM • $PF_{ingestion}$ used for oral intake • Value not presented • Source of data not presented
Jo et al. (1990)	TCM • $PF_{ingestion}$ used for oral intake, inhalation and dermal contact • TCM = 0.26 $(mg/kg\text{-}day)^{-1}$ • Published PF (upper 95% CI) derived from linearised model applied to single ingestion animal study
Attias et al. (1995)	THM4 • Unit risk used for oral intake • TCM = 0.00000027; BDCM = 0.0000046; DBCM = 0.00000304; TBM = 0.000000304 (units of risk per 1 μg/L) • Unit risks (upper 95% CI) estimated from toxicological data using multistage and linearised multistage models
Black et al. (1996)	THM4 • $PF_{ingestion}$ used for oral intake • TCM = 0.0061; BDCM = 0.062; DBCM = 0.062; TBM = 0.0079 (units of cases/person/lifetime/(mg/kg body weight/dday)) • Published PF (upper 95%): TCM, BDCM and TBM from USEPA (1994); DBCM assumed equivalent to BDCM HAAs (DCAA and TCAA) • $PF_{ingestion}$ used for ingestion pathway • DCAA = 0.11; TCAA = 0.083 (units of cases/person/lifetime/(mg/kg body weight/dday)) • PFs from Bull and Kopfler (1991)
Chung et al. (1997)	THM4 • Single pathway (presumably ingestion) PF used for oral intake, inhalation and dermal contact • TCM = 0.00000096; BDCM = 0.00000415; DBCM = 0.0000028; TBM = 0.000000415 (units of $(\mu g/L)^{-1}$) • Unit risks (95% upper bound) obtained using TOX-RISK package (multistage model fitted to animal data)
Malcolm et al. (1999)	Epidemiological data used
Havelaar et al. (2000)	Bromate • Ingestion dose–response data applied to oral intake • Point estimate for dose–response parameter for bromate = 0.0030 $kg^{2/3}/mg$ (units of renal cell cancer induction in rats per mg $KBrO_3$/(kg body $weight^{2/3}$)) • Dose–response fitted by two-stage model based on three published studies
Hsu et al. (2001)	THM4 • $PF_{ingestion}$ used for oral intake • TCM = 0.0061; BDCM = 0.062; DBCM = 0.0084; TBM = 0.0079 (units of risk per mg/kg/day) • PFs (95% upper bound) for all THM4 cited as USEPA (1999)
Sadiq et al. (2002)	TCM • $PF_{ingestion}$ used for oral intake • 0.0061 (units of mg/kg/day) • PF (95% upper bound) from IRIS database, cited as "USEPA (2001)"
Williams et al. (2002)	TCM • $PF_{ingestion}$ used for oral pathway and dermal contact; $PF_{inhalation}$ used for inhalation • $PF_{ingestion}$ = 0.0031; $PF_{inhalation}$ = 0.0019 (units of mg kg^{-1} day^{-1}) • PFs from California EPA, cited as "OEHHA (2010)"
Fehr et al. (2003)	TCM and BDCM • $PF_{ingestion}$ used for oral intake • PF values not presented • PF was specified as a) a 95% upper bound point estimate and b) a PDF • PF from WHO guidelines cited as "WHO (1993) and WHO (1998)"
Sofuoglu et al. (2003)	TCM • PF (values not presented in paper) from IRIS database, cited as "USEPA (2001)"
Lee et al. (2004)	THM4 • $PF_{ingestion}$ used for oral intake and dermal absorption. $PF_{inhalation}$ used for inhalation of TCM; $PF_{ingestion}$ used for inhalation of BDCM, DBCM and TBM. • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • $PF_{inhalation}$: TCM = 0.081 (units of $(mg/kg/day)^{-1}$) • RfDs used for oral and dermal routes for each THM • RfD: TCM = 0.01; BCDM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg/kg/day) • PF s from IRIS database, cited as both "USEPA (1999)" and "USEPA (2002)"; RfDs from USEPA, cited as "USEPA (2002)"
Tokmak et al. (2004)	THM4 • Methodology of Lee et al. (2004) is cited as the source of the cancer risk assessment methodology used, but no values for PFs or RfDs are presented, nor which PFs were used for specific pathways etc. • Authors confirmed that the same PFs and RfDs were used as in Lee et al. (2004)
USEPA (2005)	Epidemiological data used
Kavcar et al. (2006)	THM4 • $PF_{ingestion}$ used for oral pathway • TCM = 0.01 $(mg/kg/day)^{-1}$ (RfD used instead of withdrawn $PF_{ingestion}$); values of $PF_{ingestion}$ and RfD for BDCM, DBCM and TBM not presented • All PFs and RfD from IRIS database, cited as "IRIS (2005)"
Nazir and Khan (2006)	TCM • RfD used for oral pathway (recognised as having replaced $PF_{ingestion}$); however, $PF_{ingestion}$ used for dermal contact and inhalation • RfD = 0.01 mg/kg-day; $PF_{ingestion}$ = 0.0061 $(mg/kg\text{-}day)^{-1}$ for dermal and inhalation pathways • IRIS database, cited as both "US Environmental Protection Agency (1999)" and "US Environmental Protection Agency (2001)"
Uyak (2006)	THM4 • $PF_{ingestion}$ used for oral pathway and dermal contact; $PF_{inhalation}$ used for inhalation pathway (TCM only) • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • $PF_{inhalation}$: TCM = 0.081 (units of $(mg/kg/day)^{-1}$) • RfD: TCM = 0.01; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg/kg/day) • PFs and RfDs are identical to those in Lee et al. (2004); source cited as "USEPA (1999)"

Table 2 (*continued*)

Name of study	PFs/SFs/RfDs (pathway, value, citation)
Aslan and Turkman (2007)	THM4 • $PF_{ingestion}$ used for oral intake and dermal absorption. $PF_{inhalation}$ used for inhalation of TCM; $PF_{ingestion}$ used for inhalation of BDCM, DBCM and TBM. • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • $PF_{inhalation}$: TCM = 0.081 (units of $(mg/kg/day)^{-1}$) • RfDs used for oral and dermal routes for each THM • RfD: TCM = 0.01; BCDM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg/kg/day) • PFs and RfDs from IRIS database, cited as "USEPA (2002)"
Navarro et al. (2007)	THM4 • $PF_{ingestion}$ used for oral pathway for brominated THMs only; TCM excluded from cancer risk calculation • $PF_{ingestion}$ for BDCM, DBCM and TBM not presented • RfD: TCM = 0.01 mg/kg-day • IRIS database cited as "IRIS (2005)"
Semerjian and Dennis (2007)	THM4 • $PF_{ingestion}$ used for oral pathway (including TCM) and dermal contact; $PF_{inhalation}$ used for inhalation pathway • $PF_{ingestion}$: no values presented; $PF_{inhalation}$: no values presented • RfD: no values presented • Authors subsequently provided values of $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079; $PF_{inhalation}$: TCM = 0.081 • PFs and RfDs from IRIS database, cited as "USEPA (2006)"
Wang et al. (2007a)	THM4 • $PF_{ingestion}$ used for oral pathway (for THM4) and for inhalation (for BDCM and DBCM); $PF_{inhalation}$ used for TCM and TBM; PF_{dermal} used for dermal contact • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.079 (units of $(mg/kg\text{-}day)^{-1}$) • PF_{dermal}: TCM = 0.0305; BDCM = 0.0633; DBCM 0.14; TBM = 0.0132 (units of $(mg/kg\text{-}day)^{-1}$) • $PF_{inhalation}$: 0.0805; BDCM = 0.062; DBCM = 0.084; TBM = 0.00385 (units of $(mg/kg\text{-}day)^{-1}$) • $PF_{ingestion}$ (THM4) and $PF_{inhalation}$ (TCM and TBM) from IRIS cited as "IRIS (2005)"; PF_{dermal} from RAIS cited as "RAIS (2005"
Wang et al. (2007b)	THM4 • $PF_{ingestion}$ used for oral pathway and dermal contact; $PF_{inhalation}$ used for inhalation pathway • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • $PF_{inhalation}$: TCM = 0.000023; 0.0000024; 0.0000018; 0.00000023 (units of $(mg/kg/day)^{-1}$) • RfD: TCM = 0.01; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (mg/kg/day) • All PFs and RfDs from IRIS database cited as "USEPA (2005)"
Baytak et al. (2008)	THM4 • $PF_{ingestion}$ used for oral pathway (BDCM, DBCM, TBM); RfD used for TCM • $PF_{ingestion}$: BDCM = 0.0000062; DBCM = 0.084; TBM = 0.079 (units of $(mg/kg/day)^{-1}$) • RfD: TCM = 0.01; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (mg/kg/day) • PFs and RfDs from IRIS database cited as "IRIS (2007)". $PF_{ingestion}$ for BDCM is 1000 times too small. $PF_{ingestion}$ for TBM is one order of magnitude too high (perhaps this error is copied from Wang et al. (2007a)).
Viana et al. (2009)	THM4 • Type of PF used for oral, dermal and inhalation pathways not stated • No values are presented; authors subsequently confirmed that $PF_{ingestion}$ was used for oral and dermal route (BDCM, DBCM); $PF_{inhalation}$ used for inhalation (TCM); ingestion of TCM was not considered • $PF_{ingestion}$ and RfDs derived from IRIS, cited as both "USEPA (1990) and USEPA (2006)". $PF_{inhalation}$ for TCM from Williams et al. (2002)
Chowdhury and Champagne (2009)	THM4 • $PF_{ingestion}$ apparently used for inhalation and dermal contact (not made explicit) • $PF_{ingestion}$: TCM = 0.01 (RfD); BDCM = 0.062; DBCM = 0.0084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • RfD: TCM = 0.01; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg/kg/day) • PFs and RfDs from IRIS database cited as "IRIS (2006)"
Buteau and Valcke (2010)	TCM • Pathway-specific toxicological reference values (TRV) for ingestion and inhalation derived from minimal risk levels (MRL) for non-cancer effects; $TRV_{ingestion}$ also used for dermal contact • $TRV_{ingestion}$ = 0.13 (units of mg/kg/day) • $TRV_{inhalation}$ = 0.056 (units of mg/kg/day) • MRLs from ATSDR cited as "ATSDR (1997)"
Chowdhury and Hall (2010) *Retracted*	THM4 • $PF_{ingestion}$ used for oral pathway (presumably also used for dermal and inhalation routes) • $PF_{ingestion}$: TCM = 0.01 (RfD); BCDM = 0.062; DBCM = 0.0084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • IRIS database cited as "IRIS (2009)"
LaKind et al. (2010)	THM4 • Biomonitoring equivalent (BE) values for both cancer and non-cancer outcomes (note that these are only as robust as the underlying health-based exposure guidelines i.e. PFs and RfDs) • Cancer ○ BE: TCM = NA (lack of PF); BDCM = 0.15; DBCM = 0.16; TBM = 7.4 (for 10^{-6} risk level, units of pg/mL blood) • Non-cancer ○ BE_{RfD} (biomarker concentration consistent with the RfD): TCM = 230; BDCM = 20; DBCM = 80; TBM = 130 (units of pg/mL blood) ○ BE_{POD} (biomarker concentration consistent with the human-equivalent point of departure): TCM = 750; BDCM = 190; DBCM = 270; TBM = 420 (units of pg/mL blood) • BEs derived from previously published study
Basu et al. (2011)	THM4 • $PF_{ingestion}$ used for oral pathway (THM4) and inhalation (BDCM and DBCM); $PF_{inhalation}$ used for inhalation (TCM and TBM); PF_{dermal} used for dermal contact • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg\text{-}day)^{-1}$) • PF_{dermal}: TCM = 0.0305; BDCM = 0.0633; DBCM = 0.14; TBM = 0.0132 (units of $(mg/kg\text{-}day)^{-1}$) • $PF_{inhalation}$: TCM = 0.0805; TBM = 0.00385 (units of $(mg/kg\text{-}day)^{-1}$) • $RfD_{ingestion}$: TCM = 0.01; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg/kg/day) • RfD_{dermal}: TCM = 0.002; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg/kg/day) • $PF_{ingestion}$, $PF_{inhalation}$ and RfDs from IRIS database, cited as "IRIS (2005)"; PF_{dermal} from RAIS cited as "RAIS (2005)"

(*continued on next page*)

Table 2 (*continued*)

Name of study	PFs/SFs/RfDs (pathway, value, citation)
Chowdhury et al. (2011) *In italics: updates according to Chowdhury (2012) response to commentary Bull et al. (2012)*	THM4 • $PF_{ingestion}$ used for oral pathway and dermal contact (THM4), and for inhalation (BDCM and DBCM); $PF_{inhalation}$ used for inhalation (TCM and TBM) • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.0084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • $PF_{inhalation}$: TCM = 0.081; TBM = 0.0039 (units of $(mg/kg/day)^{-1}$) • PFs from IRIS database cited as "IRIS (2009)", except for TCM where already rescinded IRIS data were used • *$PF_{ingestion}$ used for oral pathway and dermal contact (BDCM, DBCM and TBM), and for inhalation (BDCM and DBCM); $PF_{inhalation}$ used for inhalation (TBM)* • *$PF_{ingestion}$: BDCM = 0.062; DBCM = 0.0084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$)* • *$PF_{inhalation}$: TBM = 0.0039 (units of $(mg/kg/day)^{-1}$)* • *PFs from IRIS database cited as "IRIS (2009)"*
Legay et al. (2011)	THM4 • $PF_{ingestion}$ used for oral pathway and dermal contact (THM4), and for inhalation (BDCM and DBCM); $PF_{inhalation}$ used for inhalation (TCM and TBM) • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.079 (units of $(mg/kg/day)^{-1}$) • $PF_{inhalation}$: TCM = 0.081; TBM = 0.0039 (units of $(mg/kg/day)^{-1}$) • $PF_{ingestion}$ from IRIS database, cited as "IRIS (2009)"; $PF_{inhalation}$ from RAIS, cited as "RAIS (2009)" • Note: for TCM 2 "scenarios" were used: 1. rescinded PF used; 2. RfD = 0.01 mg/kg/day was used DCAA • $PF_{ingestion}$ used for oral pathway • $PF_{ingestion}$ = 0.05 (units of $(mg/kg\text{-}day)^{-1}$) • PF from IRIS database, cited as "IRIS (2009)"
Liu et al. (2011)	THM4 • $PF_{ingestion}$ used for oral, inhalation and dermal contact pathways • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/(kg\ day))^{-1}$) • PFs from USEPA, cited as "USEPA (1999) and USEPA (2007)"
Pardakhti et al. (2011)	THM4 • $PF_{ingestion}$ used for oral pathway and dermal contact; $PF_{inhalation}$ used for inhalation pathway • $PF_{ingestion}$: TCM = 0.031; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg\ day)^{-1}$) • $PF_{inhalation}$: TCM = 0.0000805; BDCM = 0.13; DBCM = 0.095; TBM = 0.00385 (units of $(mg/(kg\ day)^{-1})$) • PFs from IRIS database, cited as "IRIS (2009)", and from California EPA (no citation presented)
Yamamoto (2011)	THM4 • $PF_{ingestion}$ used for oral pathway • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg)/day$) • RfD: TCM = 0.01; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg/kg-day) • PFs and RfD from uncited source
Venkataraman and Uddameri (2012)	THM4 • $PF_{ingestion}$ used for inhalation; details on other pathways not provided • $PF_{ingestion}$: TCM = 0.01 (RfD); BDCM = 0.062; DBCM = 0.0084; TBM = 0.0079 (units of $(mg/kg\ day)^{-1}$) • RfD: TCM = 0.01; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg/kg-day) • PFs and RfDs from Chowdhury and Champagne (2009)
Amjad et al. (2013)	THM4 • $PF_{ingestion}$ used for oral pathway and dermal contact; $PF_{inhalation}$ used for inhalation pathway • $PF_{ingestion}$: TCM = 0.031; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of mg kg^{-1} day^{-1}) • $PF_{ingestion}$: TCM = 0.0000805; BDCM = 0.13; DBCM = 0.095; TBM = 0.00385 (units of mg kg^{-1} day^{-1}) • RfD: TCM = 0.01; BDCM = 0.02; DBCM = 0.02; TBM = 0.02 (units of mg kg^{-1} day^{-1}) • PFs from Pardakhti et al. (2011): IRIS database, cited as "IRIS (2009)", and California EPA (no citation presented); RfDs from Lee et al. (2004)
Gan et al. (2013)	THM4 • $PF_{ingestion}$ used for oral pathway and dermal contact (THM4) and inhalation (BDCM and DBCM); $PF_{inhalation}$ used for inhalation pathway (TCM and TBM) • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • PF_{dermal}: TCM = 0.035; BDCM = 0.0633; DBCM = 0.14; TBM = 0.0132 (units of $(mg/kg/day)^{-1}$) • $PF_{inhalation}$: TCM = 0.081; TBM = 0.00385 (units of $(mg/kg/day)^{-1}$) • $PF_{ingestion}$ and $PF_{inhalation}$ from IRIS database, cited as IRIS (2005); PFdermal from RAIS, cited as RAIS (2005). The authors claim to have accessed this information in 2012, in spite of the fact that some quoted data were rescinded some years previously HAAs • $PF_{ingestion}$ used for oral pathway • $PF_{ingestion}$: DCAA = 0.05; TCAA = 0.07 (units of $(mg/kg/day)^{-1}$) • PFs from IRIS, cited as "IRIS (2005)"
Lee et al. (2013)	THM4 • $PF_{ingestion}$ used for oral pathway and dermal contact (THM4) and inhalation (BDCM and DBCM); $PF_{inhalation}$ used for inhalation pathway (THM4) • $PF_{ingestion}$: TCM = 0.0061; BDCM = 0.062; DBCM = 0.084; TBM = 0.0079 (units of $(mg/kg/day)^{-1}$) • $PF_{inhalation}$: TCM = 0.081; BDCM = 0.13; DBCM = 0.094; TBM = 0.0039 (units of $(mg/kg/day)^{-1}$) • $PF_{ingestion}$ (TCM) and $PF_{inhalation}$ (TCM and TBM) from RAIS, cited as "RAIS (2010)"; $PF_{ingestion}$ (BDCM, DBCM and TBM) from IRIS, cited as "USEPA (2011)"; $PF_{inhalation}$ (BDCM and DBCM) from Cal/EPA, cited as "Cal/EPA (2010)" but source unclear
Karim et al. (2013)	THM4 • $PF_{ingestion}$ used for ingestion and dermal contact • No values presented for PFs or RfDs • $PF_{ingestion}$ from IRIS, cited as (Lee et al., 2004), and from RAIS, cited as (Wang et al., 2007a); RfDs from USEPA, cited as (Basu et al., 2011; Lee et al., 2004) and "USEPA (1999)"

to characterise exposure through all possible pathways to all possible DBPs, which would be prohibitively resource-intensive. Importantly, estimates of LECR calculated from toxicological data on THMs alone have been shown to be some two orders of magnitude lower than those calculated from epidemiological data, where THM concentrations can be considered a surrogate for an unknown putative agent (Bull, 2012).

Where age- and sex-stratified ERFs can be derived from epidemiological data, these should be applied to the respective strata within the target population.

In spite of the results of the assessments depending heavily on the ERF data used, key information was omitted from a number of reports (Table 2). Specific PFs used in calculating carcinogenic risks were not reported in 8 studies. In several studies, PFs were quoted that would not have been in agreement with cited databases at the time of publication, or sources of data were cited so vaguely as to make verification of PFs impossible. In a few studies, no citation was provided whatsoever for these data. In other cases, the values of PFs reported (and potentially used) were incorrect. In one case, $PF_{ingestion}$ for TBM was reported an order of magnitude too high (Wang et al., 2007a) — this error appears to have been reproduced afterwards in another paper (Baytak et al., 2008). The value reported in one paper for $PF_{ingestion}$ for DBCM was an order of magnitude too low (Chowdhury and Champagne, 2009), an error that was apparently propagated into two subsequent papers (Chowdhury and Hall, 2010 (retracted); Chowdhury et al., 2011). In fact, the Chowdhury & Hall paper was retracted specifically because the IRIS RfD was erroneously used as though it were a PF (thereby completely invalidating the results), and the authors did not publish an erratum when these errors were identified. By graphically representing the $PF_{ingestion}$ from all studies (Fig. 1), it is possible to see that the same values were used by many studies over a period of 2 decades, sometimes without paying heed to updated advice regarding the use of these data. There is considerably more variation over time among the PFs used for dermal (Fig. 2) and inhalation (Fig. 3) exposure routes, perhaps partly because in studies seeking to include risk estimation for exposure DBCM and BDCM by inhalation, the authors either sought alternative data when the USEPA ceased to support their use, or continued using them regardless. The central role that dose– and exposure–response data play in population health impact assessment should not be underestimated: these data should be included in the reporting of assessments, and unambiguous citations (including the date of access in the case of online databases) provided to the sources from which they have been obtained. Full review of the validity and suitability of these data should be carried out before using them to characterise risk in a target population.

3.6. Risk characterisation

With some notable exceptions, the overwhelming majority of studies focused on estimation of cancer risks associated with DBP exposure, as might be expected given societal concerns about DBPs as possible human carcinogens. Lifetime excess risk of cancer was characterised in most studies by multiplying exposures by PFs to give lifetime cancer risks (after methodology in, for example, Anderson and USEPA Carcinogen Assessment Group, 1983; USEPA, 1986; Smith, 1996). For non-cancer outcomes, exposure was divided by RfDs to yield HQ (or their sum across pathways, hazard index (HI)). Several of the studies looking at LECR proceeded to calculate the number of lifetime excess cancer cases in a population by multiplying the estimate of LECR by the target population of interest.

Three studies used epidemiological data to assess risks in a population related to exposure to DBPs. One of these (Attias et al., 1995) estimated the incremental lifetime carcinogenic risk (or unit risk), for a hypothetical human population subjected to 1 μg/L of TTHM. This was subsequently used in the same way as a PF to predict the LECR in a population based on its exposure. The second study estimated the cases of disease (cancers of the bladder, colon and rectum, and birth defects)

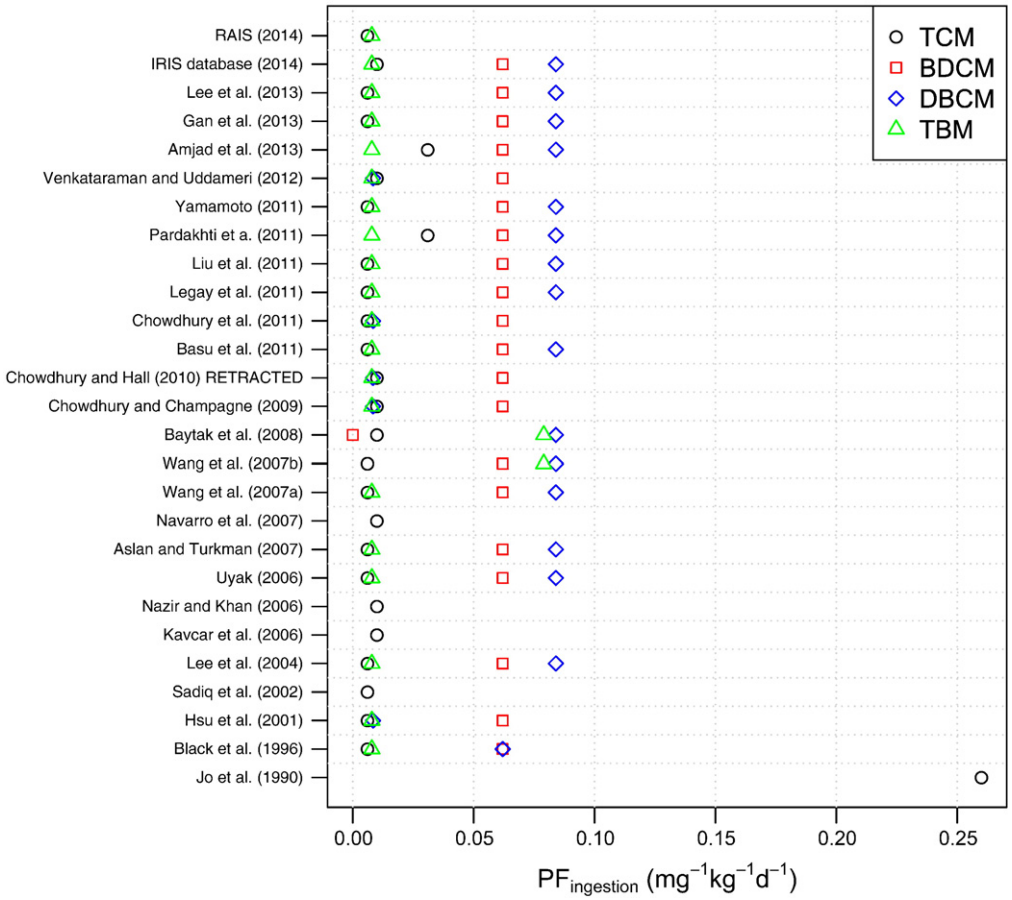

Fig. 1. Cancer potency factors for trihalomethanes used for ingestion route, by study (presented chronologically).

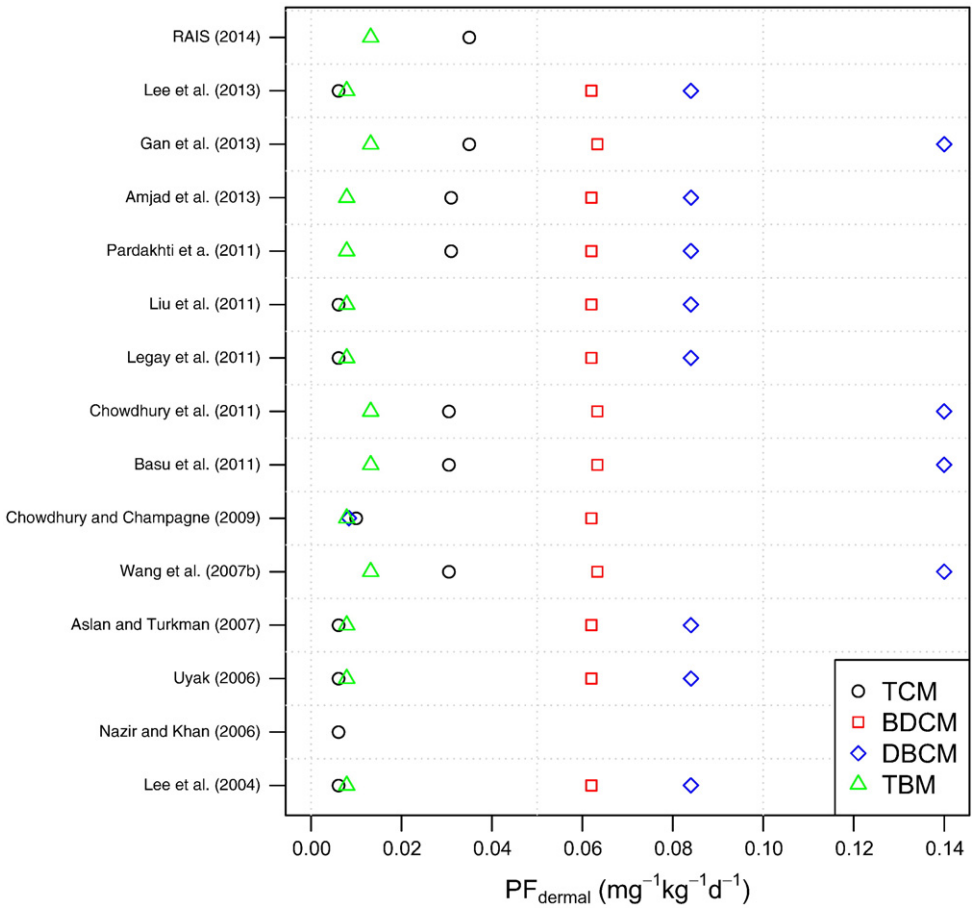

Fig. 2. Cancer potency factors for trihalomethanes used for dermal route, by study (presented chronologically).

attributable to DBP exposure (Malcolm et al., 1999) using population attributable risk percent (PAR%) using the formula:

$$PAR\% = \left[\frac{Pe(RR-1)}{1+Pe(RR-1)}\right] \cdot 100$$

where *Pe* is the proportion of the population exposed, and *RR* is the relative risk from an epidemiological study. The result was then applied to cancer registry and birth defect registry data for one year, and reported as the annual number of cases attributable to DBP contamination of drinking water. The third study (USEPA, 2005) calculated the PAR associated with exposure to DBPs and subsequently number of annual cases of bladder cancer that would be avoided after the entire population would have been exposed for a lifetime under new exposure conditions. In the one study that considered risks of microbial disease (Havelaar et al., 2000), infection from *C. parvum* was estimated using an exponential dose–response model based on volunteer data. Daily risks were cumulated over a year to provide an annual risk for the population. In order to compare between two very different kinds of disease endpoints, namely renal cell cancer and microbial disease, Havelaar et al. (2000) transformed estimates of cases of disease into disability-adjusted life years (DALYs) using clinical data relating to the severity and duration the diseases in question.

There are a number of clear advantages associated with calculating attributable risks or cases of disease using human exposure–response data. Firstly, there is no uncertainty introduced through extrapolating between species, though there are, of course, limitations to the transferability of an ERF based on epidemiological data, in particular due to differences in other factors contributing to disease (genetics or behaviours, for example), between the population from which the ERF was obtained and the target population of the assessment. Secondly, attributable cases of specific disease endpoints can be predicted in the target population, which is of considerable value to decision-makers. Thirdly, there is less of a constraint to focus on individual chemicals, for which toxicological data may be scarce, or of limited applicability to humans; exposure proxies used in the epidemiological studies may be considered to reflect overall exposure to DBPs (albeit with associated loss of precision in the risk estimates), allowing us to forego assumptions regarding the putative agent or agents in the DBP mixture.

In a number of the studies calculating LECR, upper bound risk estimates were further projected onto either hypothetical populations (Black et al., 1996; Havelaar et al., 2000; Jo et al., 1990) or, most commonly, onto the specific population of an area, region or country experiencing a particular exposure, in order to arrive at an estimate of the excess cases of cancer that could be expected in such a population in a year, or over a lifetime. One major weakness to this approach lies in the multifactorial nature of carcinogenesis, with rates for most cancers increasing dramatically with age. Given that the age structure of those target populations is not taken into account, comparisons of cases of cancer calculated in this way across different areas are likely to present a very distorted message to decision-makers. Estimates of the attributable cases of specific types cancer were presented in those studies using epidemiological data to quantify exposure–response (Attias et al., 1995; Malcolm et al., 1999; USEPA, 2005) and as such this approach ostensibly ought to provide more specific and meaningful information to decision makers. However, the estimates of preventable cancer deaths in New Zealand in 1995 published by Malcolm et al. (1999) are approximately twice as high as our own estimates for the New Zealand population in 2012 (not presented), which we calculated using relative risks from the only meta-analysis available at the time,

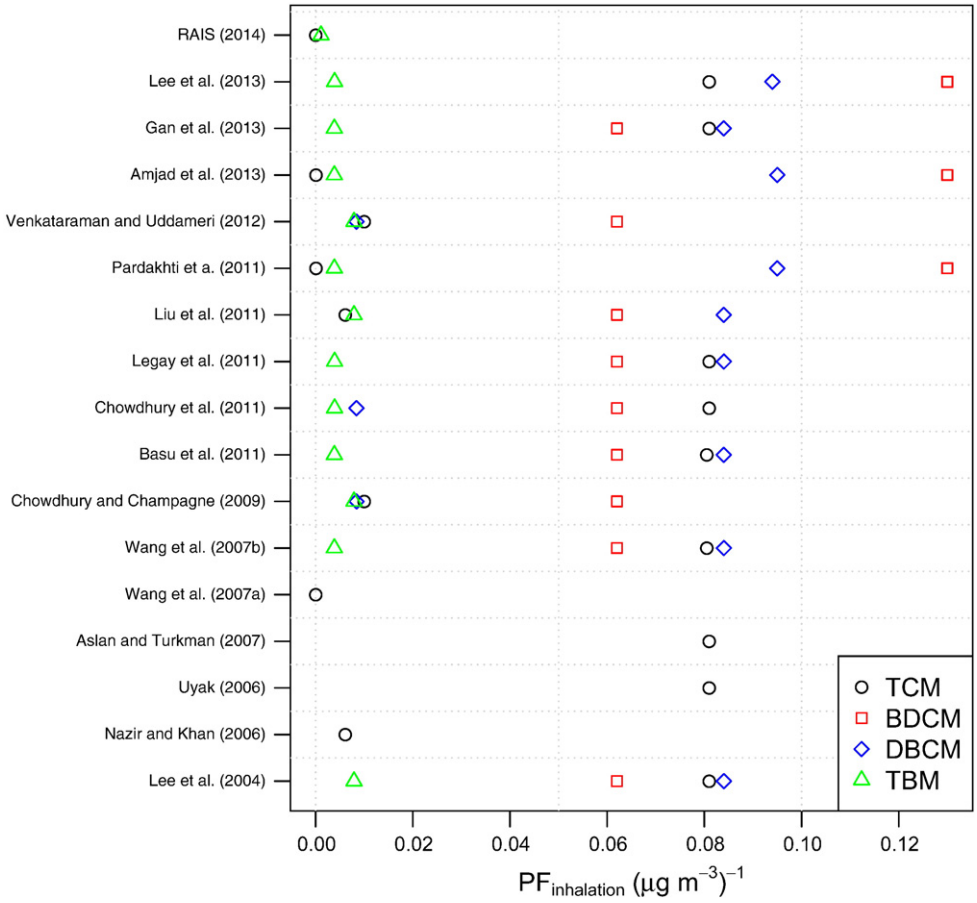

Fig. 3. Cancer potency factors for trihalomethanes used for inhalation route, by study (presented chronologically).

namely that of Morris et al. (1992). This apparent overestimation may be due to improvements in survival for bladder and colorectal cancers between 1995 and 2012. However, our own estimates of attributable burden due to colorectal cancer had wide 95% uncertainty intervals that included zero and for this reason emphasise that estimates of AF_P and attributable cases be presented with their associated uncertainty intervals. It is unclear how unit risks were calculated from relative risks in the Attias et al. (1995) study, and it is not explained in that study why more easily interpretable estimates of attributable fractions, for example, were not calculated instead.

Typically the temporal nature of a population health impact assessment is determined by time-related characteristics of the exposure data. In some cases, demographic or health data may also be used to define this temporal scope. In one study, baseline rates of bladder cancer were averaged over several decades, thereby defining the timescale of the assessment and implicitly accounting for latency of effects (Attias et al., 1995). The means by which latency and temporality were explicitly considered in the USEPA (2005) study discussed above represent an example of how to treat these issues. Some assessments that used ERFs derived from epidemiological data were purely cross-sectional in their approach, in spite of the fact that they were addressing cancers known to be characterised by long latency. In studies estimating lifetime cancer risk, a lifetime of exposure was generally fixed at 70 years; where lifetime cases of cancer were estimated for specific populations, it is hard to know exactly to *which* population such estimates should be assigned. For example, where a target population is assigned a LECR, this should be understood to be the number of excess cancer cases estimated for a population of individuals, each living for 70 years, irrespective of their current age i.e. for those of 70 years of age and older, this risk is presented for exposure in the past, for those of 69 years of age and under, the risk is presented for exposure yet to occur. Interpreting such a metric is far from straightforward given the uncertainties in past and future exposures, and limits the usefulness of such an approach. Also, this method takes no account for increases in cancer risk with increasing age. The effect of not explicitly determining the timeframe of an assessment may result in estimates of exposure and associated risk being over- or underestimated unpredictably. In general, when estimating the attributable cases of a disease in a target population, age- and sex-stratified data should be used, for example:

$$\textit{Attributable cases} = \sum_{i,j}\left[\frac{Pe_{ij}\left(RR_{ij}-1\right)}{1+Pe_{ij}\left(RR_{ij}-1\right)}\right]\cdot\frac{I_{ij}}{100,000}\cdot N_{ij}$$

where Pe_{ij} is the proportion of the target population exposed in i age groups and for j sexes, RR_{ij} is the age- and sex-stratified relative risk, I_{ij} is the annual incidence of the disease per 100,000 of the target population, and N_{ij} is the age- and sex-stratified number of people in the target population.

Cumulative exposure and latency associated with chronic health effects (e.g. time between first exposure and development of a cancer) present themselves as complex issues to the assessor. While cross-sectional modes are static, in the sense that they use current exposure and health data to estimate a burden of disease attributable to a cancer, this is not robust from a temporal standpoint. Such models do not account for the fact that cancer prevalence rates at the current time reflect past exposure to contaminants. Historic exposure data are seldom available for drinking water contaminants due to the relatively recent introduction of monitoring systems. The assessor is then faced with a trade-off between introducing uncertainties through extrapolating exposure

into the past, and extrapolating exposure and prevalence data into the future. Historic exposure to drinking water contaminants has been estimated in epidemiologic studies by using historical data on treatment type and source water to build scenarios about levels of DBPs in the past (e.g. Villanueva et al., 2004); similar approaches could be used to estimate the population health impacts under baseline conditions. Conversely, scenarios can be employed to account for the health impacts of specific decisions made today, for example regarding treatment technologies. In either case, it is important to specify precisely the target populations for which health impacts are being assessed, as well as the period of exposure and latency periods to which these relate.

Taking account of various aspects of time in population health impact assessments requires consideration of duration, frequency and temporal variability of exposure, as well as time elapsed between exposure and development of disease (latency). Where data or methods are insufficient for a thorough consideration of timing, assumptions and their associated limitations should be described. In most of the studies reviewed, the temporal nature was generally not stated explicitly, and time-related limitations were not discussed.

3.7. Scenarios

Some studies explicitly defined scenarios under which risk estimates might be compared in support of decision-making. These scenarios included different waste disposal policies (Lahey and Connor, 1983), implementation of carbon removal technologies or alternative water treatment measures (Black et al., 1996; Sadiq et al., 2002; USEPA, 2005; Wang et al., 2007b; Yamamoto, 2011), water privatisation policies (Fehr et al., 2003), and chlorination versus no chlorination (Malcolm et al., 1999). Other studies compared risks under alternative exposure scenarios, such as showering versus drinking (Jo et al., 1990), shower design parameters (Chowdhury and Champagne, 2009), shower usage (Nazir and Khan, 2006; Venkataraman and Uddameri, 2012), and consumption of bottled water versus tap water (Kavcar et al., 2006). Others compared risks related to different kinds of exposure–response data (Attias et al., 1995), or under different assumptions regarding the carcinogenicity of chloroform (Legay et al., 2011). Only one study compared the competing risks associated with disinfection: i.e. risks associated with microbial contamination and with DBPs (Havelaar et al., 2000). Multiple scenarios relating to changes in regulations and compliance were compared with three separate sets of baseline conditions in the USEPA (2005) study. Those studies that did not explicitly define scenarios presented estimates of risk associated with DBP exposure versus implied counterfactual scenarios of zero risk at zero exposure. This approach misses the opportunity of supporting relevant decision-making processes; more fundamentally, however, the implicit scenario of zero DBPs is neither plausible nor particularly useful where chemical disinfection is near-ubiquitous and serves an important purpose in controlling microbial contamination. Drastic, all-or-nothing scenarios do little to inform policy if they are not realistic.

Ideally, assessors should be guided by discussion with decision-makers so that scenarios represent actual or (realistic) potential policy questions. We were surprised to find only one study that weighed up the risks (DBPs) and benefits (drinking water free of pathogens) associated with disinfection (Havelaar et al., 2000), given the importance of such a risk–benefit analysis and the very direct implications of such research to policymakers and drinking water providers. In the most extensive study reviewed, considerations relating to microbial quality were accounted for in separate assessments used to develop the regulatory scenarios employed in the DBP assessment which did not pose microbial risks to public health (USEPA, 2005). We would argue that modelling potential effects on health of other hypothetical scenarios relating to DBPs—for example, irrespective of whether they are societally relevant or politically, technically or economically possible—is ultimately an inefficient use of scientific resources; identifying the most relevant policy questions and building realistic scenarios should form a key part of the scoping phase of any population health impact assessment. Narrowing the scope of a population health impact assessment to a single contaminant and presenting a risk only against an implicit counterfactual scenario of zero exposure may lead to inappropriate risk management decisions. The value of population health impact assessments should be seen in terms of better understanding the multiple risks in drinking water disinfection and supply so that decisions and policies might be made for the overall improvement of public health.

3.8. Analysis of uncertainty

In the context of regulatory risk assessment the use of default values and assumptions is a necessary means of achieving consistency among evaluations of different hazards. Many of the studies reviewed had used data based on similar default values and assumptions in spite of their use outside of the regulatory sphere. Such studies may produce biased results, and may underestimate uncertainty introduced, for example, for true variability in characteristics, behaviours and structure of the target population. These studies would have gained by better characterising such uncertainties; at the very least many would have benefitted from documenting possible sources of uncertainty unaccounted for and the limitations that these would impose on their results. Thorough lists of modelling assumptions, the uncertainties associated with them, and their potential effects on results were presented in very few studies.

Studies which included some analysis of uncertainty used a variety of methods, ranging from sensitivity analysis employing different values of PF, to probabilistic modelling and comprehensive sensitivity analyses of stochastic, parametric, model and data uncertainties. The USEPA (2005) study featured by far the most comprehensive approach to treat uncertainties—incorporating modelling, simulations, extensive sensitivity analyses among other approaches—a discussion of which is outside of the scope of this paper.

The influence of using different data sets, methods or models on results was investigated in some studies, by presentation of systematic univariate sensitivity analysis, or, in the majority of studies by using ad hoc methods of sensitivity analysis. In one study, exposure parameters (some of which were defined probabilistically) were systematically increased by 10% and the effect on the total absorbed dose was calculated (Buteau and Valcke, 2010). Although this approach yielded useful information regarding the system being modelled and the parts of that system on which more attention should be focused with regard to accuracy and precision, no attempt was made to assess the sensitivity of the overall assessment results to potential uncertainties in the ERF, thereby missing potentially important sources of uncertainty that might completely alter the findings of the study. Focusing all attention on the exposure side of the causal chain that is drawn between hazard, exposure and health risk—and failing to recognise the potential significance of uncertainties in the ERF in this chain—represents a serious oversight.

Probabilistic simulation techniques such as Monte Carlo analysis were used to characterise uncertainty in exposure assessment in a number of studies (see Table 1). Deterministic modelling is increasingly considered as an inappropriate means of assessing uncertain risks (Frey, 1992; Reckhow, 1994; Sander et al., 2006). Employing probabilistic simulation as a means of incorporating stochastic and parametric uncertainty into variables within the model, and propagating these uncertainties along the causal chain to the results, allow the assimilation of various input uncertainties at each step of the modelling process (Aertgeerts and Angelakis, 2003). Uncertainty in results can then be apportioned to each uncertain input variable through the use of rank correlation and importance analysis: knowing where the major uncertainties lie in the assessment model provides useful information on the areas in which additional research or investment might be

warranted. The full value of using probabilistic approaches was not exploited in some studies that characterised exposure with probability distribution functions, since PFs were still defined deterministically, in spite of the fact that they may represent a major source of uncertainty in an LECR assessment. Bootstrapping was used in exposure assessment in two studies as a means of inferring robust non-parametric probability distribution functions from limited sampling data (Sadiq et al., 2002; Sofuoglu et al., 2003). One method proposed for assessing effects on health of DBPs lacking detailed toxicity data is fuzzy synthetic evaluation (Sadiq and Rodriguez, 2004). Fuzzy sets can be parameterised using weights derived from the carcinogenicity potential ranking system, and arbitrary weights can then be assigned to these sets when they are 'defuzzified'. The advantages of this approach are that it enables a synthesis of cancer and non-cancer risks in one framework; where data are available only in non-commensurate units, vagueness in definitions can be propagated through a causal framework; and the modular form of the methodology is fully scalable to any number of possible contaminants, and health effects etc. The chief limitation of such an approach is that results are highly sensitive to the selection of weights and aggregation operators, which can usually be derived only by using expert opinion.

Population health impact assessment cannot always be a precise science. In producing a scientific answer to a real-world policy problem relating to DBPs, it is usual to make several assumptions, use data of different levels of precision, and employ methods subject to numerous caveats and limitations. These should be recorded, alternatives explored, and results presented in the context of their limitations. In general, it is worthwhile considering the degree of uncertainty of each component of the risk modelling exercise, and assessing whether these are proportional to one another. There is little to be gained from producing very precise exposure estimates if the resolution of that data is later clouded by the much poorer precision of the risk characterisation data or methods, for example.

3.9. Interpretation and presentation of assessment results — risk communication

Given the current lack of conclusive evidence of causation of health outcomes among humans exposed to DBPs, any assessment of health risks should be presented alongside a clear acknowledgement of the degree to which results depend on the assumption of causation; such information was largely absent from the vast majority of papers reviewed.

Several studies purported to estimate the cases of cancer attributable to exposure to DBPs, when in fact these estimates are characterised by large uncertainties, and determined partly by embedded value judgements that constitute a part of the regulatory risk framework-based methods and data used. In some cases, policy recommendations made by these studies are disproportionate with the results when viewed in the context the methods used. For example, some studies recommended the substitution of current disinfection treatments (chlorination) with alternatives (e.g. ozonation, chloramination) even when the number of excess cancer cases was negligible over the 70-year lifetime for which they were estimated (Aslan and Turkman, 2007; Chowdhury and Champagne, 2009). In such studies, the potential societal or economic cost implications of such changes were seldom considered, in particular in terms of the potential risks associated with alternative treatments, including other DBPs, for example.

Maps of cancer risk were presented in three studies (Karim et al., 2013; Legay et al., 2011; Venkataraman and Uddameri, 2012) and several of these were based on interpolation, using models that were very weakly supported by data. From a risk communication perspective, presenting high resolution maps of cancer risk runs the danger of masking the much lower resolution and precision of exposure data and ERFs used; the public may imagine that interpolated levels of exposure are reliable and representative of their true state of risk. Apparent spatial inequalities may be little more than artefacts of the overall modelling process.

It is crucial that adequate care is taken in the presentation of results of potentially sensitive assessments. One attributable cancer risk assessment reported that the "total cancer risk analysis indicates that Izmir residents could get cancer from the daily intake of water" (Aslan and Turkman, 2007). Such pronouncements are not helpful for policymakers and could grossly mislead the public and decision-makers. In the context of developing countries where the threat of waterborne disease is particularly serious, presenting what appears to be a scientifically irrefutable claim of disinfection as the cause of cancer may result in unfounded public alarm and bad public health decisions. Ideally, results should be presented in the context of the many uncertainties that characterise them, with recognition of the assumptions that were made to facilitate the assessment, and with due consideration of other risks associated with any recommendations made.

4. Conclusions

We reviewed 40 published studies presenting estimates of the public health impacts associated with DBPs in drinking water. With a few notable exceptions, all assessments had weaknesses which we believe seriously reduce the reliability and utility of their results. Firstly, the majority of these studies used upper bound cancer potency factors derived from animal studies to estimate generic lifetime cancer risk or cancer cases attributable to exposure to THMs, the most commonly monitored DBPs, in a particular region or city. Regulatory risk assessment methods and exposure–response data designed for these purposes are intended to overestimate risks (often by an unknown margin) so as to be protective of public health. As such, we consider them inappropriate for accurately predicting realistic levels of risk in target populations. In addition, the lack of specificity of the health outcomes predicted by such methods greatly limits their usefulness in decision-making. We would consider the use of epidemiological data derived from large, well-conducted studies to provide much more accurate, robust and scientifically rigorous estimates of risk in target populations. Many studies were limited by only the most superficial considerations of the true complexity of the occurrence, physicochemical properties and potential relative toxicity of the vast array of chemicals comprising the DBP mixture present in typical chlorinated tap water samples. Additionally, the benefits attributable to disinfection (in terms of reduction of microbial disease) were not considered in the vast majority of studies. Poor characterisation of exposure in the target population, little consideration of the temporally heterogeneous character of that exposure, and a lack of specificity in terms of health outcomes and population characteristics were identified in many of the studies reviewed. Focusing on specific DBPs in the absence of a mechanistic explanation or a true putative agent in the DBP mixture may result in inappropriate or expensive decisions being made in favour of alternative disinfection treatments that may present other health risks, a point convincingly made by Bull (2012).

In this paper we have argued that the use of inappropriate data that inflate risks should be avoided. Only through considered and transparent use of appropriate data, modelling and assumptions, can any assessment of health impacts relating to DBPs be expected to provide useful information to support policy in this area. To our mind, the population health impact assessment should be, above all, a transparent and stringent scientific exercise carried out to provide the best possible answer to a relevant policy question or risk management decision. This might consider any aspect of the system of relevance to the policy, such as possible health effects of alternative water sources, treatment methods or behaviours relating to drinking water, and should consider these in terms of other resulting changes in competing risks such as microbial contamination. The perception that population health impact assessment can be carried out as a simple add-on to an exposure assessment study greatly limits the usefulness of the assessment results. Currently, we consider that, with very few exceptions, existing studies add very little to our understanding of public health implications of DBP exposure,

and their results could unnecessarily cause alarm among the public which might lead to poor decisions being made by policy-makers and drinking water providers. Future studies should focus on answering real-world policy questions regarding the quality of drinking water, including consideration of both microbial and chemical parameters. They should use up-to-date, appropriate and robust data and methods to answer these questions, and be transparent in explaining the various uncertainties that affect their results, including their quantification where appropriate. While we recognise that the tremendous effort and resources employed by USEPA (2005) in conducting an economic assessment are not typically available to small groups of researchers working in this field, many of the principles underlying that approach can and should be adopted in all health impact assessments relating to DBPs.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2015.02.003.

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