40 years on: what do we know about drinking water disinfection by-products (DBPs) and human health?

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ABSTRACT

2014 marks the 40th anniversary of the seminal discovery by Johannes Rook, in 1974 that trihalomethanes (THMs) were formed by the chlorination of natural organic matter (NOM) in drinking water. Since this discovery, which revolutionized how we viewed drinking water safety and quality, hundreds of other classes of disinfection by-products (DBPs) have been discovered. The finding in 1976 by the U.S. National Cancer Institute that chloroform, the dominant THM, was a rodent carcinogen spurred a large number of epidemiology and toxicology studies into chlorinated drinking water. In 1985, this cancer finding was shown to be wrong. We should now be asking: What do we know about the human health impacts of DBPs in drinking water? Bladder cancer has been the most consistent finding from epidemiologic studies in North America and Europe and the possibility that chlorinated drinking water contributes an increased risk of bladder cancer remains a viable hypothesis. Despite some recent improvements in exposure assessments to focus on inhalation and dermal exposures rather than ingestion, no causal agent with sufficient carcinogenic potency has been identified, nor has a mechanistic model been validated. Consequently, a sensible precautionary approach to managing DBPs remains the only viable option based on four decades of evidence.

Key words | causation, chloroform, precaution, rationale, risk trade-off, trihalomethanes, uncertainty

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LIST OF ABBREVIATIONS

BDCM   bromodichloromethane

CH   choral hydrate

CxDBP   chlorination disinfection by-product

DBAN   dibromoacetonitrile

DBCM   dibromochloromethane

DBP   disinfection by-product

DCAA   dichloroacetic acid

DCAN   dichloroacetonitrile

HAA5   sum of 5 haloacetic acids -MCAA, DCAA, TCAA, monobromoacetic acid (MBAA) and dibromoacetic acid (DBAA)

MCAA   monochloroacetic acid

NDMA   *N*-nitrosodimethylamine

NOM   natural organic matter

TBM   tribromomethane, bromoform

TCAA   trichloroacetic acid

TCP   trichlorophenol

THM   trihalomethane

THM4   sum of chloroform, BDCM, DBCM and TBM

INTRODUCTION

The year 2014 provided a major anniversary in the history of drinking water quality and safety assessment. In 1974, the Dutch water chemist, Rook (1974) published his seminal discovery that trihalogenated methanes (THMs) are formed by the reaction of chlorine used to disinfect drinking water (inactivate pathogenic microorganisms) and natural organic matter (NOM). This discovery was soon followed by the publication of Bellar *et al.* (1974) who independently made the same discovery in the USA This single discovery forever changed how we look at drinking water quality and has led to the subsequent discovery of hundreds of other unintended

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by-products of essentially all disinfection processes. These contaminants are now broadly termed, disinfection by-products (DBP).

There have likely been many thousands of research papers published on various aspects of DBP and drinking water (e.g., a June 2014 Web of Science search turned up over 12,000 citations for only a few of the relevant key words), countless graduate students trained and certainly several billions of dollars of investment in technology, monitoring and research over the past 40 years. There have clearly been major, undeniable benefits of all this research activity and investment in yielding improved understanding of drinking water treatment processes, better drinking water quality in terms of both safety and aesthetic quality and an overall higher level of evidence-based understanding for the provision of safe drinking water. However we should be willing to ask how well the past 40 years of research has improved our understanding of the nature and extent of any human health impacts associated with DBPs in drinking water.

This paper seeks to provide a high level overview of some of the major issues about chlorination DBPs and human health over the 40 year timeline before reflecting on our current state of knowledge and what can reasonably be anticipated in the coming decade. This focus on chlorination DBPs has been chosen because chlorine-based disinfection processes are still the most widely practiced and these are generally the most cost-effective for smaller systems that are resource-constrained. Our focus in this overview discussion of 40 years of research and regulation of DBPs necessarily emphasizes toxicology evidence and risk assessment rather than epidemiology. This emphasis is necessary because epidemiologic studies of drinking water are not able to establish mechanisms of toxic effect attributable to specific DBPs that invariably occur as complex mixtures. Likewise, it is outside our scope to engage in a detailed comparison and critique of the strengths and weaknesses of toxicology vs. epidemiology.

MATERIAL AND METHODS

This discussion is directed only at organic DBPs and emphasizes those produced by disinfection processes involving chlorine. Such DBPs may or may not contain chlorine (e.g., NDMA) and for the purposes of this discussion will be termed CxDBPs. The discussion is based on a distillation of the perspectives gained from performing a series of comprehensive literature reviews over the past decade (Hrudey 2008, 2009), participation on several international expert panels (e.g. Mills *et al.* 1998; Arbuckle *et al.* 2002; Sinclair *et al.* 2002; Hrudey *et al.* 2003; Hrudey *et al.* 2012, 2014) on **Q1** issues relating to DBPs and human health over the past 17 years, co-editing (authoring or co-authoring several chapters) for this book – *Disinfection By-Products and Human Health* (Hrudey & Charrois 2012).

RESULTS AND DISCUSSION

The short format allowed for these papers does not allow for comprehensive or detailed review of this subject, but more detailed discussions may be found elsewhere (Hrudey 2008, 2009, 2012a; International Interdisciplinary Expert Panel 2015). The following relies on a few illustrative examples to demonstrate the larger issues.

Initial concerns about adverse health effects possibly attributable to drinking water exposure to DBPs initially focused on cancer. This was initially driven by the coincidence that chloroform was declared a carcinogen in 1976 by the U.S. National Cancer Institute (NCI 1976). Less than 10 years later, evidence was published (Jorgenson *et al.* 1985) to demonstrate that the original rodent tumour results were an artefact of the bioassay experimental protocol caused by delivering near-lethal doses of chloroform dissolved in corn oil as a daily bolus (by gavage) into the animal gut leading to a massive liver tumour response. The later work delivering extremely high doses (900,000 μg/L rats, 1,800,000 μg/L mice) of chloroform to the rodents via drinking water produced no detectable tumour response. Related research established that chloroform is not genotoxic (does not damage DNA) and that the original bioassay results were the result of massive localized tissue damage caused by the high chloroform exposure delivered by the corn oil vehicle. More than 10 years later, the U.S. EPA proposed in 1998 to recognize this evidence and to treat chloroform as a threshold carcinogen (i.e. a substance capable of causing tumours at exposures only above a

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specified level; in such cases there is no validity to using a cancer slope factor, CSF, to estimate cancer risk), but this proposal was withdrawn until a court judgement obtained by the chlorine industry ordered the U.S. EPA to follow the requirements of the U.S. Safe Drinking Water Act (SDWA), i.e. to use the best available science (Pontius 2000). Ironically, at trial the U.S. EPA acknowledged the threshold mode of action. The U.S. regulatory changes regarding chloroform as a carcinogen were proposed in 2003 and finally adopted in 2006.

The increasing WHO guideline numbers for chloroform (30 µg/L in 1984, then 200 µg/L in 1993, then 300 µg/L in 2011; Table 1), reflect the changing understanding (declining concern) for chloroform in drinking water as cancer risk. The numbers for THM provide a different story even though chloroform is the dominant THM in most waters, unless bromide levels cause substantial formation of brominated THMs.

Another interesting development evident in Table 1 was the Health Canada guideline for BDCM in 2006 that was withdrawn in 2009. Our expert panel (Hrudey et al. 2003) had suggested that Health Canada should take a closer look at BDCM because it potentially posed a reproductive risk concern, but the 2006 MAC of 16 µg/L was calculated using a CSF for a cancer bioassay done on BDCM that also suffered from using the corn oil daily bolus dose regimen. When a new study for BDCM was published (NTP 2006) using drinking water, BDCM-dosing failed to support the rodent cancer risk at concentrations up to 700,000 µg/L, Health Canada to its credit, convened an expert panel to review its BDCM guideline and retracted it.

The rationale for maintaining THM4 levels much lower than harmless levels of chloroform is not articulated clearly by drinking water agencies. Presumably it reflects caution about brominated THM species, where they occur, because they may pose a greater health risk (WHO 2005; Health Canada 2009). Perhaps it reflects the concern that within the overall large number of CxDBPs there may be issues and reducing these using THMs as a surrogate is desirable, particularly within the bounds of achievability. Unfortunately, this lack of clarity has led to considerable confusion among water practitioners about whether chloroform, as the dominant THM, poses a cancer risk via drinking water exposure (Hrudey 2012b). Several audience surveys were conducted in the past 2 years, with varying degrees of formality and structure with operational personnel in Australia and Canada to determine their understanding about whether THM regulatory levels are based on cancer risk posed by chloroform. Responses ranged from over 50% to as high as 80% who believe that THM levels in drinking water are set to protect against cancer risk from chloroform, with the second largest response being 'don't know'. Only a small minority of respondents knew that chloroform in drinking water does NOT pose any cancer risk. Who can blame the majority for believing in a chloroform cancer risk in the absence of any clear communications on this issue by regulators?

Certainly, the research literature is not helpful in providing clarity for readers on this topic. Chowdhury & Hall (2010) published predictions of cancer cases for Canadian cities that claimed to use a CSF for chloroform from the U.S. EPA IRIS database (checked in 2009) except that the CSF had been removed from IRIS in 2001. Ultimately, the Chowdhury & Hall (2010) paper was retracted by the journal, but another paper (Chowdhury et al. 2011), was published in another journal using similar erroneous cancer case calculations for each Canadian province. This one avoided claiming use of a CSF from the U.S. EPA IRIS database, instead the journal editors allowed the authors to use a CSF from an unspecified source, describing it only as a 'previously published value.' The 2011 paper made the additional error of presenting CSF-based risk predictions (which are 70-year lifetime risks) as being annual cancer risk predictions. This paper attracted a commentary exchange (Bull et al. 2012) to reveal its errors. Drinking water professionals busy with the job of producing quality drinking water cannot be expected to keep track of such exchanges and should question the quality of the research literature peer review process for such cases.

Despite the confusion about chloroform, there is a viable hypothesis that CxDBPs in drinking water may cause human bladder cancer (Hrudey 2012a; International Interdisciplinary Expert Panel 2015). This possibility is based on bladder cancer showing the greatest consistency as a cancer outcome that is statistically associated with human exposure to chlorinated drinking water in up to 10 epidemiological studies of varying predictive quality and statistical power. Because of this possibility, the case for

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Table 1 | Drinking water guidelines for organic disinfection by-products (DBPs)[a]

Date[b]	Jurisdiction or agency	Initiative	Comment
1978	Health Canada	THM4 350 µg/L	MAC, guideline, not to exceed
1979	U.S. EPA, Safe Drinking Water Act (SDWA)	THM4 100 µg/L	MCL, regulation, running annual average
1984	World Health Organization (WHO)	Chloroform 30 µg/L	MAC, guideline, not to exceed
1993	WHO	Chloroform[c] 200 µg/L	MAC, guideline, not to exceed
		TBM 100 µg/L	MAC, guideline, not to exceed
		DBCM 100 µg/L	MAC, guideline, not to exceed
		BDCM 60 µg/L	MAC, guideline, not to exceed
		TCP 200 µg/L	MAC, guideline, not to exceed
1996	Australia, National Health & Medical Research Council (NHMRC)	THM4 250 µg/L	MAC, guideline, not to exceed
		MCAA 150 µg/L	MAC, guideline, not to exceed
		DCAA 100 µg/L	MAC, guideline, not to exceed
		TCAA 100 µg/L	MAC, guideline, not to exceed
		CH 100 µg/L (2014)	MAC, guideline, not to exceed
1996	Health Canada	THM4 100 µg/L	MAC, guideline, running annual average, quarterly samples
1998	U.S. EPA, SDWA	THM4 80 µg/L HAA5 60 µg/L	MCL, regulation, system-wide running annual average, quarterly samples
1998	EC Drinking water directive	THM4 100 µg/L	MCL at the point of delivery as a maximum in each sample. Requirement to achieve lower if possible by improving treatment.
2003 to 2004	WHO	DCAA 50 µg/L	MAC, guideline, not to exceed
		DCAN 20 µg/L	MAC, guideline, not to exceed
		DBAN 70 µg/L	MAC, guideline, not to exceed
		MCAA 20 µg/L	MAC, guideline, not to exceed
		TCAA 200 µg/L[d]	MAC, guideline, not to exceed
2006	U.S. EPA, SDWA	THM4 80 µg/L HAA5 60 µg/L	MCL, regulation, locational running annual average, quarterly samples - to include locations with highest concentrations
2006	Health Canada	BDCM 16 µg/L	MAC, guideline, not to exceed
2006	WHO	NDMA 0.10 µg/L	MAC, guideline, not to exceed
2008	Health Canada	THAA (HAA5) 80 µg/L	MAC, guideline, running annual average, quarterly samples
2009	Health Canada	BDCM withdrawn[e]	New NTP cancer bioassay for BDCM
2011	Health Canada	NDMA 0.04 µg/L	MAC, guideline, not to exceed
2011	Australia, NHMRC	NDMA 0.10 µg/L	MAC, guideline, not to exceed
2011	WHO	chloroform 300 µg/L[f]	MAC, guideline, not to exceed

[a]All abbreviations are explained in list of abbreviations following references.
[b]Earliest date adopted. Later dates are only shown if the number has changed with later updates.
[c]The recognition that chloroform was not genotoxic led to a threshold cancer risk assessment.
[d]MAC value increased because TCAA weight of evidence is judged not to be genotoxic.
[e]The result of a 2006 National Toxicology Program (NTP) bioassay on BDCM removed the basis for the risk calculation by finding no evidence of cancer risk for BDCM administered in drinking water.
[f]MAC value increased because of a larger proportion of exposure assigned to water, noting that other uses of chloroform have decreased substantially since the previous MAC set in 1993.

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continuing research and sensible precautionary management of CxDBPs in drinking water clearly remains justified, particularly the removal of precursor NOM which should reduce most CxDBPs. However, this precautionary rationale needs to be effectively articulated by regulators and other authorities.

The site-specific (bladder) cancer epidemiology risk estimates are orders of magnitude greater than the upper bound, non-site specific cancer risk prediction for any known carcinogenic CxDBP. Some will argue that since CxDBPs are always present as a mixture there could be synergistic interactions. However, at such low concentrations there is little evidence that this is possible and the most likely outcome would be additive effects from substances with similar mechanisms of action or even target organs. However, in view of the small concentrations even simple additivity is not likely to result in the massive increase in toxic effects that would be required to match the epidemiological risk estimates.

Bull (2012) explored the evidence about bladder cancer for those DBPs that have sufficient evidence to have a published CSF available. Not even the sum of risk from all the carcinogenic CxDBPs with CSFs, yields a total cancer risk prediction remotely (within 100 fold) close to the magnitude of the cancer risk indicated by the bladder cancer epidemiology. Bull et al. (2011) have explored this discrepancy by considering other classes of DBPs that are more plausible carcinogens, but so far even considering these new DBPs

fails to close the gap between toxicological risk assessment estimates and epidemiologic estimates for bladder cancer that might be caused by DBPs.

The scope of this short paper does not allow for adequately exploring the evidence in support of a causal relationship between exposure to CxDBPs and adverse reproductive outcomes. However, as a generalization, the human evidence on reproductive impacts of CxDBPs is less consistent than it is for a possible causal association with bladder cancer (Nieuwenhuijsen et al. 2009, 2010).

Figure 1 provides a rationale to address the reality that contaminants detected in drinking water are not equally risky to human health. Even judging concentrations of any substance detected in relation to its established guideline or regulatory value does not provide the entire meaningful perspective. As evident in Table 1, different jurisdictions have judged the same health research evidence on a DBP to yield different criteria. But, more important, not all contaminants that could pose a health risk in drinking water at sufficiently high concentration have done so, except possibly in extreme spill or direct poisoning episodes, or the comparative confidence that is evident for high levels of drinking water arsenic causing cancer (IARC 2004).

For the specific case of DBPs, the possible human health risks that have been suggested in some cases (e.g., bladder cancer) have apparent risk magnitudes that certainly warrant attention, but the level of confidence which can be placed in the evidence for actual human risks via drinking
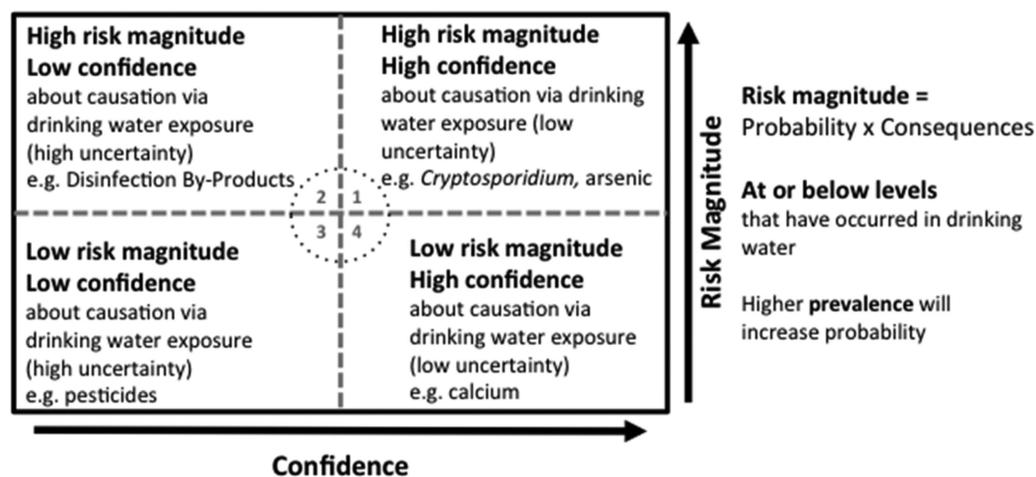
Q4 **Figure 1** | Disinfection by-products assessed according to a rationale showing two key dimensions of any risk of a drinking water contaminant causing any serious adverse human health effect (adapted from Hrudey et al. 2012).

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water is vastly lower than the established certainty that microbial pathogens cause human illness via drinking water exposure. Only microbial pathogens and a relatively short list of chemical contaminants like arsenic, fluoride and possibly nitrates/nitrites and selenium have caused documented cases of human illness via drinking water exposure (WHO 2007).

An issue that seems to influence common perceptions of the CxDBP and human health issue regards an inability for some to distinguish between mere detection of a substance and the existence of a human dose of that substance sufficiently high to cause a health effect.

Figure 2 is a simple graphical illustration of the toxicologists' 'creed': *the dose makes the poison – all substances are toxic in sufficient dose* using the widely experienced toxic substance, ethanol. About 400 mL of pure ethanol would be lethal to a person of average body mass. Toxic effects of ethanol occur for daily consumption of concentrations above about 10^{23} molecules/L but we are mostly able to tolerate and repair this 'damage'. However, the completely harmless level of ethanol in fresh, pure orange juice (mean ~400 ppm or 5×10^{21} molecules/L, Nisperos-Carriedo & Shaw 1990) is a 100 fold lower and concentrations down to a million times lower can be detected by routine analysis. Given sufficient investment, much lower concentrations could be found. In principle, as little as 1 molecule (10^0) could be detected in a litre of water. Hopefully, no one is likely to defend a case that

detection of 1 molecule of ethanol per litre of water poses a health risk. The key point that many of our colleagues will say they recognize but which they may not truly believe is that mere detectability of a substance tells us nothing about likely human health impacts of negligibly small exposures.

Only knowing how much exposure to a toxic substance exposure occurs relative to the amount proven necessary to cause a human toxic effect can tell us anything meaningful about the likelihood of adverse human health impacts.

The past 40 years of experience with DBPs have demonstrated that our collective ability to detect substances in water has totally outstripped our capability to judge the human health risk posed. We can be certain that the lower end of the range of newly detected DBPs will continue toward the right of Figure 2. Currently, we are only half way down the scale. We have already moved detectability of water contaminants about 7 decades (10,000,000 fold) down that scale in the past 50 years. Completing the journey to detecting one molecule per litre will not likely take another 50 years.

CONCLUSIONS

Overall, the discovery of DBPs in drinking water has been positive in driving research to improve drinking water quality and optimize disinfection and other treatment
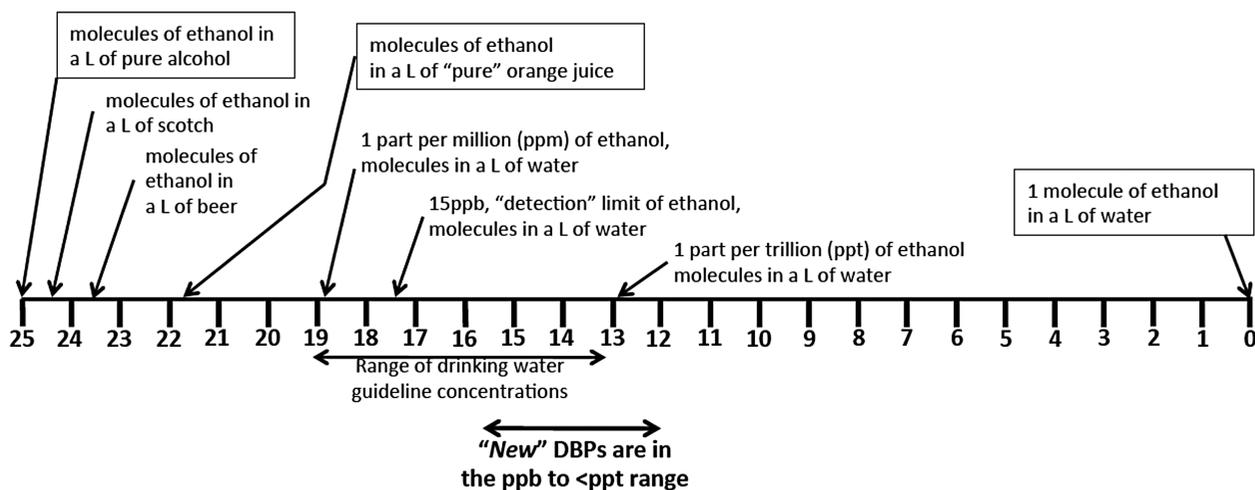
Figure 2 | The Dose Makes the Poison – An illustration, best read from left to right, of the enormous range of concentrations (requiring a logarithmic scale). Concentrations are presented as molecules per litre (shown as powers of 10) of substances found in drinking water using ethanol, a well-documented toxic substance, as the example.

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processes because of the implied risk trade-off between DBPs and pathogens, but as with any situation involving balancing of risk, there has been continuous tension.

There will be inevitable discovery of more DBPs in drinking water, but this reality need not pose any human health risk contrary to a common 'popular' view implicitly held by too many of our colleagues; simple detection of any in drinking water provides no evidence about the likelihood of causing human health effects. The real challenge is to find ways to improve our ability to judge whether any of the CxDBPs that are detectable in drinking water pose any human health risk. Concluding that CxDBPs must cause human health effects because they are 'toxic' substances, is untenable. Authentic evidence concerning human health risks for the longest known DBPs remains uncertain. However, the dominant CxDBP, chloroform, essentially poses no cancer risk in drinking water at levels below about a few hundred µg/L.

Moving forward, a sensible, precautionary approach is necessary, whereby currently known technologies to manage DBPs are applied as part of overall water quality management systems. However, extraordinary measures to reduce DBPs or abandon chlorine-based disinfection are currently not justified. Likewise, arbitrary measures to reduce one or more classes of DBP must NOT be implemented without full understanding of what different DBPs or other water quality problems may result from technology change. Above all, management of DBPs must remain a much lesser concern than the essential requirement of assuring that drinking water is adequately and consistently disinfected at all times.

REFERENCES

Arbuckle, T. E., Hrudey, S. E., Krasner, S. W., Nuckols, J. R., Richardson, S. D., Singer, P., Mendola, P., Dodds, L., Weisel, C., Ashley, D. L., Froese, K. L., Pegram, R. A. *et al.* 2002 Assessing exposure in epidemiologic studies to disinfection by-products in drinking water: Report from an International Workshop. *Environmental Health Perspectives* **110** (Supp 1), 53–60. [Q2]

Bellar, T. A., Lichtenberg, J. J. & Kroner, R. C. 1974 The occurence of organohalides in chlorinated drinking waters. *Journal American Water Works Association* **66** (12), 703–706.

Bull, R. J. 2012 Toxicological evaluation of experimental data that informs the magnitude of cancer risk from disinfection by-products. In: *Disinfection By-Products and Human Health*, (S. E. Hrudey & J. W. A. Charrois eds). IWA Publishing, London.

Bull, R. J., Reckhow, D. A., Li, Xingfang, Humpage, A. R., Joll, C. & Hrudey, S. E. 2011 Potential carcinogenic hazards of non-regulated disinfection by-products: haloquinones, halo-cyclopentene cyclohexene derivatives, N-halamines, halonitriles, heterocyclic amines. *Toxicology* **286**, 1–19.

Bull, R. J., Fawell, J., Cotruvo, J. & Hrudey, S. E. 2012 Critique of Chowdhury *et al.* (2011). *Journal of Hazardous Materials* **237–238**, 382–383.

Chowdhury, S. & Hall, K. 2010 RETRACTED. Human health risk assessment from exposure to trihalomethanes in Canadian cities. *Environment International* **36**, 453–460.

Chowdhury *et al.* 2011 Disinfection byproducts in Canadian provinces: associated cancer risks and medical expenses. *Journal of Hazardous Materials* **187**, 574–584. [Q3]

Health Canada 2009 Guidelines for Canadian Drinking Water Quality:Guideline Technical Document. Trihalomethanes. (May 2006 with April 2009 addendum). http://hc-sc.gc.ca/ewh-semt/pubs/water-eau/trihalomethanes/index-eng.php.

Hrudey, S. E. 2008 *Chlorination disinfection by-products in drinking water: A primer for public health practitioners reviewing evidence from over 30 years of research*. National Collaborating Centre for Environmental Health. http://www.ncceh.ca/sites/default/files/Chlorination_Disinfection_By-Products_2008.pdf.

Hrudey, S. E. 2009 Chlorination disinfection by-products, public health risk tradeoffs and me. *Water Research* **43**, 2057–2092.

Hrudey, S. E. 2012a Epidemiological inference and evidence on DBPs and human health. Chapter 11. 213–282. In: *Disinfection By-Products and Human Health*, (S. E. Hrudey & J. W. A. Charrois eds). IWA Publishing, London.

Hrudey, S. E. 2012b Disinfection By-Products and Human Health. Watermark, B.C. *Water and Wastewater Association* **21** (2), 30–31.

Hrudey, S. E. & Charrois, J. W. A. Eds. 2012 *Disinfection By-Products and Human Health*. IWA Publishing, London. May 2012. 324 pp.

Hrudey, S. E., Bathija, A., Bull, R. J., Dodds, L., Jenkins, G., King, W., Murphy, P., Narotsky, M., Reif, J., Savitz, D. & Thomas, B. 2003 *Executive Summary. International Expert Workshop for Health Canada to Identify Critical Endpoints for Assessment of Health Risks Related to Trihalomethanes (THMs) in Drinking Water*. March 2003.

Hrudey, S. E., Fawell, J., Leiss, W., Rose, J. B. & Sinclair, M. 2012 *Managing Uncertainty in the Provision of Safe Drinking Water*. Canadian Municipal Water Consortium, Canadian Water Network. University of Waterloo. http://www.cwn-rce.ca/assets/resources/pdf/managing-uncertainty-in-the-provision-of-safe-drinking-water.pdf

IARC 2004 *Some Drinking Water Disinfectants and Contaminants, Including Arsenic. IARC Monographs on the*

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Evaluation of Carcinogenic Risks to Humans. Vol 84. IARC scientific publications, International Agency for Research on Cancer, Lyon, France.

International Interdisciplinary Expert Panel 2015 *Evidence for Association of Human Bladder Cancer with Chlorination Disinfection By-Products.* Water Research Foundation, Denver, CO.

Jorgenson, T. A., Meierhenry, J. R., Rushbook, C. J., Bull, R. J. & Robinson, M. 1985 Carcinogenicity of chloroform in drinking water to male Osborne-Mendel rats and female B6C3F1 mice. *Fundamental & Applied Toxicology* **5**, 760–769.

Mills, C. J., Bull, R., Cantor, K., Reif, J., Hrudey, S. E., Huston, P. & an Expert Working Group. 1998 Health risks of drinking water chlorination byproducts: report of an expert working group. *Chronic Diseases in Canada* **19** (3), 91–102.

NCI 1976 *Carcinogenesis Bioassay of Chloroform.* National Cancer Institute, Bethesda, MD, U.S.A.

Nieuwenhuijsen, M. J., Grellier, J., Smith, R., Iszatt, N., Bennett, J., Best, N. & Toledano, M. 2009 The epidemiology and possible mechanisms of disinfection by-products in drinking water. *Philosophical Transactions of the Royal Society A.* **367**, 4043–4076.

Nieuwenhuijsen, M. J., Grellier, J., Iszatt, N., Martinez, D., Rahman, M. B. & Villanueva, C. M. 2010 Literature review of meta-analyses and pooled analyses of disinfection by-products in drinking water and cancer and reproductive health outcomes. Chap. 24, 483–496. In: *Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations*, (R. U. Halden, ed.). ACS Symposium Series, American Chemical Society.

Nisperos-Carriedo, M. O. & Shaw, P. E. 1990 Comparison of volatile flavor components in fresh and processed orange juices. *Journal of Agricultural and Food Chemistry* **38** (4), 1048–1052.

NTP 2006 *Toxicology and Carcinogenesis Studies of Bromodichloromethane (CAS No. 75–27–4) in Male F344/N Rats and Female B6C3F1 Mice (Drinking Water Studies).* National Toxicology Program, ResearchTriangle Park, NC.

Pontius, F. W. 2000 Chloroform: science, policy and politics. *Journal American Water Works Association* **92** (5), 12, 14, 16, 18.

Rook, J. J. 1974 Formation of haloforms during chlorination of natural waters. *Water Treatment and Examination* **23**, 234–243.

Sinclair, M., Bull, R., Froese, K., Hrudey, S. E., Nieuwenhuijsen, M. & Rizak, S. 2002 *Disinfection By-Products and Health Effects. Summary of an International Expert Workshop.* CRC for Water Quality and Treatment. Occasional Paper No. 5. Salisbury, South Australia.

WHO 2005 Trihalomethanes in Drinking-water. Background document for development of WHO *Guidelines for Drinking-water Quality.* http://www.who.int/water_sanitation_health/dwq/chemicals/THM200605.pdf.

WHO 2007 *Chemical safety of drinking-water: Assessing priorities for risk management.* World Health Organization. www.who.int/water_sanitation_health/dwq/dwchem_safety/en/index.html.

Author Queries

Q1   Hrudey *et al*. (2014) is not listed in the reference list. Please add it to the list or delete the citation.

Q2   Please provide all author names for reference Arbuckle *et al*. (2002).

Q3   Please provide all author names for reference Chowdhury *et al*. (2011).

Q4   In supplied Figure 1 is not sufficient print quality. Please resupply as a high resolution file (300 dpi or above) with sharp lines and text.