Science Dossier

Human health aspects of halogenated organic by-products from use of active chlorine

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15. Environmental safety of halogenated organic by-products from use of active chlorine (May 2010)
16. Aquatic environmental risk assessment of hexachlorobenzene (September 2014)
17. Human Health aspects of halogenated organic by-products from use of active chlorine (January 2017)

Summary

This dossier reviews published literature on halogenated disinfection by-products and their potential impact on human health. Since the early 1970s, (when water treated with chlorinated biocides was noted to contain traces of chloroform and trihalomethane) several other organic, halogenated molecule families have been found in disinfected water for drinking, cleaning and recreational purposes. It is suspected that some of these molecules carry a degree of health risk.

Whilst trihalomethane and haloacetic acid are formed in the greatest quantities of all halogenated organic disinfection by-products (DBPs), other families of DBPs are also present alongside increasing numbers of 'emerging DBPs' which are being discovered as analytical methods improve. It is further suspected that over half of the organic halogen load remains unidentified as sparsely-halogenated, non-biologically active macromolecules, which are difficult to define structurally but whose properties are easily described. Their relative formation conditions are discussed in this dossier.

The World Health Organisation has characterised each of these chlorination DBP 'families' in terms of their hazards and IARC have commented on the potential carcinogenicity of these molecules, with no single DBP being classified as a *confirmed* human carcinogen. These findings are elucidated in this dossier alongside any other hazards associated with these molecules, tested both *in vivo* and *in vitro*.

The level of DBP exposure is a major factor in determining the risks associated with these hazards, with this depending on the relevant concentration and the duration of exposure. Given the potential exposure to DBPs from potable water, showering/ bathing, swimming pool/ spa water and cleaning waters, published levels of each of the targeted DBP families are discussed here. This dossier notes though that all other uses create lower potential exposure than that occurring from consuming around 2l of water per day. Critical issues are good pool management and swimmer hygiene to reduce the formation of DBPs and adequate warnings on cleaning products (e.g. to avoid mixing of bleach with acids or ammonia).

Results from epidemiological studies are also investigated (testing the associations between DBP exposure and cancer, reproductive effects and respiratory issues). For drinking water, the main conclusion is that whilst there is some evidence of an association between DBPs and bladder cancer, the causal nature is inconclusive; even after 15 years of data collection. For pool water, the oft-cited link between DBPs and asthma also lacks consistency with the advantages of swimming under hygienic, well-managed pool conditions outweighing the potential risks of toxicity; which is well understood by authorities. This lack of definite causal link is also noted for cleaning-related chlorination DBPs.

Further, whilst epidemiological data contains some findings suggesting associations with specific reproductive or developmental endpoints, there are identical studies showing no such effect. The most recent reviews conclude that only minor effects from very high doses are evident during pregnancy and even then, overall data are conflicting and inconclusive.

The dossier draws conclusions consistent with the World Health Organisation who continue to emphasise that standards of protection of potable water must not be compromised because of concerns about potential risks from disinfection by-products. The evidence summarised in this dossier fully supports the correctness of this view and, given the generally lower exposures involved, supports a similar conclusion in relation to use in protecting against infection in swimming pools and other areas. The benefits of active chlorine in protecting against infectious disease through its widespread use to disinfect drinking water, swimming pools, surfaces and other items are clear, as are the grave consequences of neglecting such use.

About the author

John Pickup, who qualified as a chemist, spent over 20 years in the chemicals and detergents industries before establishing in 1994 a consultancy specialising in scientific issues, particularly the human and environmental safety of chemicals and downstream products.

The potential health and environmental impacts of by-products of active chlorine use have been an ongoing focus of his consultancy work since its inception and he was heavily involved in dealing with these by-products during the EU Risk Assessment of sodium hypochlorite

Table of contents

1. Introduction 7

2. Organohalogen Disinfection by-product families 8

Trihalomethanes (THMs) 8

Haloacetic acids (HAAs) 8

Halogenated aldehydes, ketones and acetonitriles 9

Halofuranones 9

Inorganics 9

Chloramines 10

Emerging DBPs 10

'Unknown' DBPs 11

3. Overview of the hazards of DBPs in the context of different uses 11

4. By-product exposures from different uses 15

4.1 Potable Water 15

4.2 Pools 18

4.3 Cleaning 20

4.4 Comparable human exposures from 'other' household water uses and swimming pools. ... 20

5. Epidemiological evidence relating to possible adverse effects from different uses 23

5.1 Drinking Water 23

5.2 Pools 26

5.3 Cleaning 28

6. Conclusions 29

7. References 33

FORMULAE, ACRONYMS and ABBREVIATIONS

AOX	Adsorbable Organic Halogen	MCA	Monochloroacetic acid
BDCM	Bromodichloromethane	mg/l	milligrams per litre
BWT	Birth Weight	mg/m^3	milligrams per cubic metre
$CHCl_3$	Chloroform	MIMS	Membrane-induction Mass Spectrometry
$CHBrCl_2$	Bromodichloromethane	mmol/kg	millimoles per kilogram
$CHBr_2Cl$	Chlorodibromomethane	MX	3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone
$CHBr_3$	Bromoform	ng/l	nanograms per litre
COC	Committee on Carcinogenicity	NDEA	Nitrosodiethylamine
DBPs	Disinfection by-products	NDMA	Nitrosodimethylamine
DBCM	Dibromochloromethane	NO	Nitrogen monoxide
DCA	Dichloroacetic acid	NPYR	Nitrosopyrrolidine
DPD	N,N diethyl-1,4 phenylenediamine sulfate	OR	Adjusted Odds Ratio
DOC	Dissolved organic carbon	PTB	Pre-term birth
EIB	Exercise Induced Broncospasm	RAR	Risk Assessment Report
EU	European Union	RD50	Respiratory Rate Decrease 50%
FGR	Foetal Growth Restriction	SGA	Small for Gestational Age
g/l	Grams per litre	TCA	Trichloroacetic acid
HAA	Haloacetic acid	THM	Trihalomethane
HAN	Haloacetonitrile	THMBr	Brominated trihalomethanes
IARC	International Agency for Research on Cancer	TOC	Total Organic Carbon
IPCS	International Program on Chemical Safety	TOX	Total Organic Halogen
kDa	kilo Dalton	UK	United Kingdom
l	litre	USA	United States of America
LBW	Low Birth Weight	US EPA	United States Environment Protection Agency
LOAEL	Lowest Observed Adverse Effect Level	UV	Ultraviolet
µg/l	micrograms per litre	WHO	World Health Organisation
µg/kg	micrograms per kilogram		

1. Introduction

The use of active chlorine for disinfecting drinking water to make it safe to drink, on which almost the entire developed world relies, has saved countless lives and is suggested to be one of the most important public health advances of modern times. Its parallel use in disinfecting swimming pools and spas is similarly of crucial importance in protecting human health. Further, households and healthcare settings worldwide also rely on active chlorine's unmatched disinfection properties to protect against the risks of transmission of infectious disease.

In the 1970s however, Rook (1974) discovered that water treated with active chlorine contained traces of chloroform and other trihalomethanes (THMs). It was subsequently shown that these, and many other trace by-products, arise from reactions between the applied active chlorine and natural organic matter that can be present in substantial quantities in raw waters (though this is dependent on the water source).

The discovery of THMs in drinking water coincided with animal studies, at the maximum tolerated doses that were practiced at the time, suggesting that chloroform was a potential carcinogen. Other studies had suggested higher mortality from cancer amongst those consuming disinfected drinking water abstracted from river water (Mississippi) than from groundwater sources (Harris *et al.*, 1974).

As such, the suspicion that drinking chlorinated water may carry unsuspected chronic health risks, despite its proven benefits, has led to decades of scientific effort to understand and characterise any possible concerns.

Concurrent public *environmental* fears about halogen-containing organics contributed to a selective focus on organohalogen by-products despite innumerable oxidation by-products being produced by *all* oxidising biocides (i.e. not just active chlorine). Research has subsequently identified several hundred organohalogen by-products, mostly present in very low quantities, totalling in the order of 1 mg/l (as Cl) in drinking water.

Today however, more than 40 years after the initial discovery of disinfection by-products (DBPs), the principal DBPs remain *potential* rather than *proven* human carcinogens. The epidemiological studies, though sometimes individually suggestive of increased chronic disease risk, are often conflicting and have not yielded convincing evidence to demonstrate causation of such diseases from these ubiquitous uses.

Despite this, around the world, regulation to control DBPs continues to be based on a solely precautionary approach. Though it is sensible to work at minimising exposure and suspected associated risks, the World Health Organisation (WHO) emphasises that such efforts must never be allowed to compromise disinfection as this would expose people to the proven and very real dangers of infectious disease. Indeed, many lives continue to be lost in outbreaks of these diseases when adequate standards of disinfection are not met.

This dossier reviews the range of currently understood DBPs, and provides an overview of the numerous factors affecting their formation in the context of the three principal public health uses of active chlorine (disinfecting drinking water, pool water and 'cleaning'). A more detailed account of the underlying chemistry is contained in the accompanying Euro Chlor Science Dossier on the environmental safety of these DBPs (Euro Chlor, 2010). Both of these dossiers look at the strands of research that have investigated the formation of disinfection by-products (DBPs) and how to reduce them, their health and environmental hazards, exposure and potential risks.

This dossier focuses more on those epidemiological studies that have searched for evidence of increased cancer risk and reproductive problems from the use of potable water, as it has been suggested that showering and bathing may also be important exposure routes.

The health-related hazards and other properties of DBPs are therefore reviewed, again in context of the different uses. This dossier then sets out what is known about levels of exposure to the various DBPs arising from the different uses which indicate, in conjunction with the hazard data, whether significant risks could be expected.

Finally, this dossier reviews the currently assembled evidence from the numerous epidemiological studies that have been conducted over the decades to assess whether, and to what extent, exposure to DBPs might be adding to the burden of the various chronic diseases, particularly where such a link has been suggested.

The conclusions currently proposed by the available scientific evidence are summarised at the end of this dossier.

2. Organohalogen Disinfection by-product families

The halogenated organic by-products formed in the greatest quantities in essentially all current uses of active chlorine are the trihalomethanes and haloacetic acids. Various 'second tier' by-product families, (haloacetonitriles, haloaldehydes, haloketones and halophenols) are commonly present at an order of magnitude lower concentration, and so-called 'emerging by-products' are present typically at concentrations of orders of magnitude lower still. The different DBP families, their properties and formation conditions are discussed below.

Trihalomethanes (THMs)

The four trihalomethanes based on chlorine or bromine (i.e. chloroform ($CHCl_3$), bromodichloromethane ($CHBrCl_2$), chlorodibromomethane ($CHBr_2Cl$) and bromoform ($CHBr_3$)) can all be formed during the various uses of active chlorine solutions. In most scenarios, where bromide concentrations are low, chloroform is the dominant THM, accounting for >90% of total THMs. Concentrations usually decrease in the order $CHCl_3$ > $CHBrCl_2$ > $CHBr_2Cl$ > $CHBr_3$ (Krasner *et al.*, 1989).

THMs are volatile with relatively low solubility in water with both volatility and solubility decreasing in the same order $CHCl_3$ > $CHBrCl_2$ > $CHBr_2Cl$ > $CHBr_3$. It is noteworthy that even though THM levels in drinking water are now regulated in many countries, since the DBP investigative process began in the late 1970s, THM levels have been reduced due to changes in treatment technology including the introduction of chloramination and pre-treatment to reduce precursors.

Haloacetic acids (HAAs)

Dichloro- and trichloroacetic acids (DCA and TCA respectively) generally dominate amongst the nine different chlorinated/ brominated acetic acids that can be formed in water treated or used with active chlorine solutions. As for the THMs, when there are substantial bromide concentrations present, brominated species are more prevalent and can predominate (Nissinen *et al.*, 2002).

Increasing chlorine dose increases the formation of TCA over MCA (monochloroacetic acid) and DCA, and chlorinated HAAs rather than brominated ones (Singer 1994), though it should be noted that TCA tends to arise via separate precursors and pathways to DCA rather than forming directly from DCA by further substitution (Xie, 2003).

Haloacetic acids are relatively polar, non-volatile, water soluble species. Solubility in water at normal temperatures is of the order of 1,000 g/l for TCA increasing to 6,000 g/l for MCA whilst DCA is a miscible liquid.

Halogenated aldehydes, ketones and acetonitriles

The earliest recognised haloaldehyde from water treated with active chlorine was chloral hydrate (trichloroacetaldehyde). It is often the most prevalent haloaldehyde; lower substituted aldehydes only being measured more recently with the development of reliable analytical standards. Levels of haloaldehydes are typically an order of magnitude below THMs and HAAs, though they can be higher in specific conditions with chloral hydrate sometimes being the most abundant DBP after THMs and HAAs. Chloroacetaldehydes predominate when chloroform is the most abundant THM, whilst brominated variants increase as bromide content rises (though not to the same extent as with THMs; Koudjonou and LeBel, 2006).

Haloacetaldehydes are not chemically stable in water at typical-use pH with brominated derivatives being even less stable than chlorinated ones. Stability decreases as pH and temperature increase and the trihalo- species, which hydrolyse to the corresponding THMs, are more stable than the dihalo- derivatives (Koudjonou and LeBel, 2006).

1,1-dichloropropanone and 1,1,1-trichloropropanone are often the most abundant of the halogenated acetones and higher ketones formed during use of active chlorine (Meier *et al.*, 1985). Haloketones typically account for <1% of the total halogenated by-products and their formation decreases with rising pH and temperature.

Both haloketones are relatively volatile, and tend to be hydrolytically unstable, undergoing base-catalysed hydrolysis via the haloform reaction to generate THMs. Levels in drinking water distribution systems often decrease sharply (Krasner *et al.*, 1989).

Haloacetonitriles are also relatively volatile and susceptible to hydrolysis, via haloacetamides, to form haloacetic acids. Here, the rate of hydrolysis rises with increasing pH and number of halogen atoms in the molecule (Glezer *et al.*, 1999). The mono-derivatives are the most volatile and bromo-derivatives are less volatile, but more stable. Haloacetonitrile levels in chlorinated drinking water are typically an order of magnitude lower than THM levels and comprise <5% of total halogenated by-products. The dihaloacetonitriles are normally the most abundant, and dibromoacetonitrile can predominate where bromide levels are high.

Halofuranones

MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone) was the first of a family of furanones displaying potent bacterial mutagenic activity to be discovered (in ng/l quantities) in chlorinated drinking water (Kronberg *et al.*, 1988). Onstad *et al.* (2008) suggest that as formation patterns in a survey of US plants were observed to mimic those of THMs and HAAs, formation probably proceeds by similar mechanisms to natural organic matter. In addition, brominated analogues are produced in greater abundance than MX in high-bromide content waters. High levels of dissolved organic carbon (DOC) favour furanone formation, but chloramination has been suggested to stabilise any furanones once formed. Pre-treatment with ozone and biologically-active granular activated carbon minimized formation of these furanones upon subsequent chlorination/ chloramination.

Inorganics

Chlorate, and to a lesser extent chlorite and bromate, can be present in hypochlorite solutions that are increasingly used as an alternative to gaseous chlorine in disinfecting water. Use of chlorine dioxide as a disinfectant also results in substantial levels of chlorate and chlorite. Ozone use can produce chlorate and, in bromide-containing waters, results in bromate formation (alongside hypobromous acid and hypobromite).

Chloramines

Chloramination disinfection technology, which emerged from efforts to control THM production, may involve separate dosing of ammonia and chlorine, or of separately prepared chloramines. In either case, monochloramine is the target disinfectant. Chloramines may also be formed as by-products of chlorination in the presence of (amino-)nitrogen. In raw water this may arise from ammonia or amino acids for example, and in swimming pools from urine, sweat etc. Where Cl_2 is present in excess with respect to amino groups, di- and trichloramine will be formed.

Emerging DBPs

In recent years, a series of 'emerging DBPs' have been observed in treated waters including iodo-THMs and iodo-HAAs, halonitromethanes and nitrosamines, as summarised by Krasner (2009). Partly this trend reflects advancing analytical techniques, but the formation of additional by-products is also encouraged by increasing use of lower quality raw waters (e.g. high bromide and iodide, algal organic matter) and water re-use. In addition, changes in disinfection technology to reduce regulated by-products (THMs, HAAs) by using (e.g.) chloramines, chlorine dioxide, ozone and ultraviolet (UV), may increase the formation of some of the emerging by-products.

Iodo-THMs were amongst the first of the 'emerging DBPs' to be discovered. They mainly tend to occur at significant levels where raw waters have high levels of total organic carbon (TOC), bromide and/ or iodide; such as those influenced by seawater or saline deposits.

In raw waters with high bromide and/ or iodide levels, chloramination favours the formation of iodinated DBPs because chloramines, with less oxidizing power than chlorine, allow hypoiodous acid to accumulate and react with organic matter to form them (Bichsel and von Gunten, 2000). Krasner (2009) has commented that the yield of iodinated DBPs generally follows the order chloramines (NH_2Cl) > chlorine dioxide (ClO_2) > chlorine (Cl_2) >> ozone (O_3).

Use of chlorine for disinfection with a free chlorine residual tends to favour the production of fully chlorinated aldehydes (e.g. trichloracetaldehyde). Using chloramination however, with a chloramine residual, often predominantly produces dichloracetaldehyde. Thus, in a study of two plants treating water from the same aquifer, a chlorine-based water treatment plant produced 13 µg/l of trichloro- and 3 µg/l of dichloroacetaldehyde, whereas the plant using ozone/ chloramines produced 0.3 µg/l of trichloro- and 12 µg/l of dichloroacetaldehyde (Krasner *et al.*, 2006). Pre-ozonation can increase formation of some halonitromethanes (Krasner *et al.*, 2006), as may medium-pressure ultraviolet (UV) (Kashinkunti *et al.*, 2006, Shah *et al.*, 2012)

Formation of nitrosamines in drinking water has been observed since the introduction of chloramination. The extent of formation and even the effect of different disinfection treatments vary markedly according to the source water and, in particular, the precursors that it contains. Nitrosodimethylamine (NDMA) is generally the most frequently detected nitrosamine and the one present at highest concentrations; it is also present at significant levels in many source waters before disinfection (Zhao *et al.*, 2008). Recent studies in the context of proposed regulation of nitrosamines have, however, suggested that when more advanced analytical techniques are applied to give a more comprehensive measurement of all nitrosamines, NDMA may contribute as little as 5% of the total nitrosamine species present (Dai and Mitch, 2013).

Chloramination, or chlorination in the presence of free ammonia, tends to produce higher levels of nitrosamines than chlorination with no free ammonia. Nitrosamine levels can more than double in the distribution system (Krasner, 2009). Other oxidants, such as chlorine dioxide and ozone, can also produce nitrosamines, though they can sometimes reduce nitrosamine formation potential by destroying certain precursors. UV more often reduces nitrosamine formation, but in some circumstances can create other precursors (Zhao *et al.*, 2008, Shah *et al.*, 2012).

Nitrosamine precursors are reported as being introduced from certain materials used in drinking water treatment including cationic polymers (such as polydiallylammonium chloride; Mitch *et al.*, 2009), and from certain ferric salt coagulants (Dillon *et al.*, 2012). Raw waters impacted by wastewater effluents also tend to have higher nitrosamine formation potentials due to the range of precursors that may be present (Krasner, 2009).

As would be expected, nitrosamines are also present in aquaria, swimming pools and hot tubs, often at higher levels than those encountered in drinking water. In a survey of 27 pools and aquaria, Walse and Mitch (2008) found that temperature, precursor load, whether the pool was indoor or outdoor, and the disinfection process, affected the nitrosamine levels. Hot tubs had NDMA concentrations an order of magnitude higher than was typical for pools.

'Unknown' DBPs

As efforts have proceeded to identify more halogenated organic by-products from disinfection processes, it has frequently been remarked that a large proportion, perhaps half of the organic halogen 'load' (measurable as total organic halogen, TOX, or adsorbable organic halogen, AOX), remains unidentified. Whilst this may be *literally* true, it is expected that much of these 'unknown' organohalogens are comprised of sparsely-halogenated organic macromolecules, such as humic and fulvic acids derived from decaying vegetation that is often present in raw waters. Such macromolecules are highly complex and difficult to define structurally even in their natural state, although their properties can be extensively described.

In a study designed specifically to characterise these 'unknown' organohalogen DBPs (here defined as everything *except* THMs and HAAs), Reckhow *et al.* (2007) demonstrated that most of the DBPs detected using the TOX methodology are mid-molecular sized (0.5-10 kDa). Such macromolecules are not expected to be biologically active.

3. Overview of the hazards of DBPs in the context of different uses

Potential health hazards from disinfection by-products first came to the fore in the mid-1970s following the Rook (1974) publication. This showed chloroform formation which Symons (1975) built on, confirming the presence of a wider range of trihalomethanes in chlorinated water. Rodent cancer bioassays then suggested that chloroform displayed a carcinogenic potential (NCI, 1976), closing the 'hazard loop'. As chloroform had historically been widely used, not only as an anaesthetic but also in consumer products such as toothpaste, these papers ignited popular opinion leading to a suite of similar studies.

It is noteworthy that these early rodent studies followed protocols which applied doses close to the maximum tolerated level; effectively several orders of magnitude *higher* than the likely exposure of humans via drinking water. Based on these early studies though, the toxicity of DBPs has been subsequently comprehensively reviewed by the WHO International Program on Chemical Safety (IPCS) in 2000 and the overview below summarises their conclusions.

Trihalomethanes (THMs)

Trihalomethanes exhibit cytotoxicity (toxicity to cells) in the liver and kidneys of rodents at doses of the order of 0.5 mmol/kg body weight; though this depends on the 'vehicle of administration'. For example, administered in corn oil at high doses over long periods, the THMs can variously

induce tumours at different sites; bromodichloromethane (BDCM) being able to induce tumours in liver, kidneys and the intestine, and at lower doses than the other THMs.

IPCS (2000) commented that "cancer following chronic exposure is the primary hazard of concern for the trihalomethanes". They further noted that "chloroform is not considered a DNA-reactive mutagenic carcinogen; it can induce cancer in animals only at high, cytotoxic doses and the brominated THMs are only weakly mutagenic". IPCS thus considers that "it is clear that exposures to low concentrations of chloroform in drinking-water do not pose carcinogenic risks."

The THMs have little reproductive and developmental toxicity, but BDCM has been shown to reduce sperm motility in rats consuming 39 mg/kg of body weight per day in drinking-water.

Haloacetic acids (HAAs)

Haloacetic acids exhibit various toxicological effects in laboratory animals, and carcinogenic, reproductive and developmental effects have been observed. Nevertheless, dichloroacetate salts are used therapeutically and have been considered as potential anti-cancer agents because of their cellular-level activity. The potential for neurotoxic side effects is of concern though in such therapeutic applications. Carcinogenicity seems to be limited to the liver and to high doses; the likely mechanism involving modification of cell division and death processes rather than the (much weaker) mutagenicity. TCA and DCA are considered to have the potential to act as tumour promoters alongside other agents. IPCS comments that "the induction of mutations by DCA is very improbable at the low doses that would be encountered in chlorinated drinking-water. Furthermore, treatment of rats with high levels of TCA in drinking-water does not induce liver tumours. These data strongly suggest that TCA presents little carcinogenic hazard to humans at the low concentrations found in drinking-water". Whilst there are less data on brominated acetic acids, doses required to induce liver cancer in mice seem to be of the same order as for those of chlorinated acids.

The toxicological endpoint of concern for haloacetic acids though is the potential for developmental effects; however, animals appear to tolerate artificially created TCA concentrations in drinking water of 500 mg/l (about 1000 times typical regulatory limits) with little or no indication of adverse effects. Dibromoacetic acid has shown effects on male reproduction in animal studies (at an order of magnitude lower dose) including increased spermatid retention and atrophy of seminiferous tubules.

Halogenated aldehydes, ketones and acetonitriles

Some of these substances have toxic, carcinogenic or other hazardous properties at high doses. For example, chloral hydrate can induce necrosis of the liver in rats, and liver tumours in mice, but at concentrations several orders of magnitude higher than those occurring in drinking water. The latter effect may be due to its metabolites (TCA and DCA), which can act as tumour promoters. Chloral hydrate is used therapeutically as a sedative because of its ability to depress the central nervous system.

Some halogenated aldehydes and ketones are suggested to be potent bacterial mutagens and chlorinated propanones can induce chromosomal damage. The most potent tumour initiator in the group appears to be 1,3 dichloropropanone. IPCS conclude that there is a potential carcinogenic hazard associated with halogenated aldehydes, with chloroacetaldehyde appearing able to produce liver tumours at less than cytotoxic doses. Nevertheless, chloral hydrate, often the most abundant haloaldehyde/ ketone in chlorinated water, is evaluated as Group 3 by IARC, (i.e. 'not classifiable as to its carcinogenicity to humans').

Various haloacetonitriles show carcinogenic and mutagenic properties in short term tests but IARC considers the evidence insufficient to classify them as animal carcinogens.

Halofuranones

MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone) is the most important in a family of related halofuranones as, in animal studies, it displayed the ability to induce thyroid and bile duct tumours. *In vitro* studies show MX to be a potent mutagen in bacterial and mammalian test systems. Various studies further suggest that MX might account for up to 57% of the mutagenicity observed in *in vitro* tests of drinking water. A WHO assessment of the evidence in 2004, however, considered it remained uncertain as to whether MX is genotoxic *in vivo*, particularly at the low doses present in drinking water. IARC classifies MX as Class 2B; *possibly carcinogenic to humans*.

Inorganics

In addition to the halogenated organics, which have been the main focus of research into disinfection by-products, ions such as chlorate, chlorite and bromate (that can be present/ formed in disinfected drinking waters, including those treated with 'alternative technologies'), also have hazards and could pose risks to health.

Chlorite and (to a lesser extent) chlorate, exert toxic effects through oxidative damage (e.g. on red blood cells). However, chlorite does not increase tumours in laboratory animals in chronic exposure studies and chlorate does not appear to be teratogenic or genotoxic *in vivo*. In rats, bromate causes renal tubular damage, induces tumours in various organs in chronic studies, and is genotoxic at high doses. IPCS (2000) considered there were insufficient data to show whether bromate-induced tumours in animals are the result of genotoxicity, cytotoxicity or other mechanisms.

Chloramines

Studies on ingestion of chloramines by human male volunteers in concentrations up to 15 mg/l produced no clinical abnormalities. In addition, no reproductive or developmental effects have been associated with monochloramine which is used, through chloramination, as a drinking water disinfectant (IARC, 2004). An assessment by IARC (2004) found inadequate evidence for carcinogenicity in humans and animals and chloramine is assigned to Group 3; *not classifiable as to its carcinogenicity to humans*.

However chloramines are respiratory irritants. Though all chloramines are volatile, trichloramine (being much-less water soluble) is released much more quickly from swimming pool water for example (300 times faster than monochloramine and 100 faster than dichloramine). Trichloramine also acts more rapidly than chlorine as a sensory irritant. Measured as the time taken to produce a 50% decrease in the respiratory rate in mice, the RD50 for trichloramine was 2.5 ppm (12.3 mg/m^3) and occurred after 10 minutes whereas for chlorine it was 3.5 ppm (10.2 mg/m^3) occurring after 45-60 minutes (Gagnaire *et al.*, 1994). WHO has set a provisional guideline for chlorine species (expressed as trichloramine in air) in pools of 0.5 mg/m^3 (WHO, 2006).

Emerging disinfection by-products

Numerous other families of disinfection by-products that can sometimes be present at very low levels in drinking water have been identified, and the trend of discovery continues as analytical techniques advance. As the discoveries increase, there is greater recourse to *in vitro* tests (e.g. cytotoxicity, bacterial mutagenicity) to give an indication of the possible biological activity of by-products and/ or mixtures. While such tests can be valuable indicators as part of an investigatory programme, they have substantial limitations and caution is needed to avoid inappropriately extrapolating *in vitro* indications to statements about potential toxic, genotoxic (etc.) effects on a population.

Iodo-acids and halomethanes were among the first 'emerging' by-products to be identified. *In vitro* testing of iodo-acids from drinking water samples (derived from source waters with a high bromide/ iodide concentration that was disinfected with chloramines; Plewa and Wagner, 2004) and a subsequent study of 5 iodo-acids and 2 iodo-THMs (Richardson *et al.*, 2008) concluded that iodo-DBPs tend to have enhanced mammalian cell cytotoxicity and genotoxicity compared to their chlorinated and brominated analogues.

Bull *et al.* (2011) have attempted a more systematic approach to considering the potential carcinogenic hazard of emerging DBPs and prioritising them for further research. Using a combination of literature data on related compounds and a quantitative structure-activity relationship programme, they suggested that haloquinones, and certain halocycloalkene derivatives, might have chronic lowest observed adverse effect levels (LOAELs) in the low µg/kg/day range and should be prioritised ahead of organic chloramines and halonitriles. The authors predicted haloacetamides were likely to have similar toxicological properties to the dihaloacetic acids.

Emerging disinfection by-products

Around eight nitrosamines, found in ng/l quantities in drinking water, display genotoxic carcinogenicity in rodent bioassays. Two, NDMA and nitrosodiethylamine (NDEA) are classified as *probable* human carcinogens (IARC group 2A), whilst others are classified as *possible* carcinogens (2B). Some (for example NDMA) are relatively toxic to animals (e.g. oral LD_{50} rat 23-40 mg/kg bw; WHO, 2002) whereas others, such as nitrosopyrrolidine (NPYR), are of low toxicity (rat oral LD_{50} 900 mg/kg bw; WHO, 2008).

Concentration estimates for 10^{-5} cancer risk level ranging from 2 ng/l for NDEA and 7 ng/l to 160 ng/l for NPYR have been published in the US EPA IRIS database (USEPA, 1997, Dillon *et al.*, 2012). However, WHO (2008) set a guideline value of 100 ng/l for NDMA based on an upper bound excess lifetime cancer risk of 10^{-5} using similar large studies of liver tumours in rats but with different methodologies and defaults.

Table 1 below summarises the current IARC classification of the principal disinfection by-products as regards to their potential carcinogenicity. It shows that no DBP has been classified as a *confirmed* human carcinogen and only two are currently regarded as *probable* human carcinogens. The remainder are considered *possible* human carcinogens or have insufficient evidence to support any classification to their carcinogenicity.

Table 1 Summary of current IARC classification of DBP carcinogenicity

DBP	Animal Evidence	Human Evidence	Overall Classification
THMs (Trihalomethanes)			
• Chloroform	Sufficient	Insufficient	2B
• BDCM	Sufficient	Insufficient	2B
• DBCM	Limited	Insufficient	3
• Bromoform	Limited	Insufficient	3
HAAs (Haloacetic acids)			
• DCA (Dichloroacetic acid)	Sufficient	Insufficient	2B
• TCA (Trichloroacetic acid)	Sufficient	Insufficient	2B
• DBA (Dibromoacetic acid)	Sufficient	Insufficient	2B
• Bromochloroacetic acid	Sufficient	Insufficient	2B
Chloral Hydrate	Sufficient	Insufficient	2A
Chloroacetonitriles	Insufficient	-	3
Bromochloroacetonitrile	Insufficient	Insufficient	3
Dibromoacetonitrile	Sufficient	Insufficient	2B
MX (chlorofuranone)	Limited	Insufficient	2B
N-Nitrosodimethylamine	Sufficient	Insufficient	2A
Chloramine	Insufficient	Insufficient	3

Key: Group 1 Carcinogenic to humans
Group 2A Probably carcinogenic to humans
Group 2B Possibly carcinogenic to humans
Group 3 Not classifiable as to its carcinogenicity to humans

4. By-product exposures from different uses

This section will detail the three main uses of disinfected water and the key DBPs that may form in each setting.

4.1 Potable Water

The concentration of DBPs in potable water varies according to source water and treatment technology. Groundwaters, with low organic content can produce very low levels of DBPs upon chlorination, whilst surface waters (which contain high levels of natural organic matter) produce much higher levels. A key aspect of treatment technology that has risen greatly in importance in recent decades is pre-treatment to reduce levels of organics and, as such, DBP precursors.

Around 57% of potable water in the EU is estimated to be sourced from groundwater (Premazzi *et al.*, 1997), though that proportion varies widely across Europe. In Austria and Denmark for example, up to 99% of potable water came from groundwater, whilst in Spain and Ireland, <20% came from groundwater. Most other European countries use more 'equal' combinations of both sources.

THMs and HAAs are invariably the dominant DBPs in potable water, accounting typically for up to half of the total (with THM levels most often higher than HAA levels). Halogenated aldehydes, ketones and acetonitriles are typically present at an order of magnitude lower, collectively accounting for just a few percent of total DBPs. Several hundred more DBPs have been identified (often referred to as 'emerging' by-products) but these are present at concentrations of one or more orders of magnitude lower. It is frequently remarked that up to 50% of the total DBPs remain 'unknown', with much of this likely to be a complex array of sparsely-halogenated natural organic substances. Reckhow *et al.* (2007) concluded that most of those DBPs detected using the TOX methodology (apart from THMs and HAAs), are mid-range in molecular size (0.5 - 10 kDa), and resemble halogenated fulvic acid molecules with little fragmentation. These are substantially modified with greater densities of hydrophilic groups (carboxylic acids).

Trihalomethanes (THMs)

Since 2008, there has been a regulatory limit in the European Union (EU) of 100 µg/l set by Directive 98/83/EC, for total THMs (measured at the customer's tap, as the concentration of THMs often increases along the distribution system due to ongoing reactions with the chlorine residual). Historically, levels were often higher, and from 2003 there was an interim limit of 150 µg/l in place though several EU countries have lower standards. Groundwater sources are almost always <20 µg/l at the tap and often fall below 5 µg/l (Techware, 1996, Arora *et al.*, 1997).

In 2002, an EU Commission survey (Techware, 2002) found mean levels in seven European cities to range from 3.5 µg/l (Florence, Italy) to 170 µg/l (Huelva, Spain), with levels up to 232.7 µg/l. Most cities were within the 100 µg/l limit. The EU HIWATE study across 11 locations between March and June 2010 (Jeong *et al.*, 2012) found three locations had THM levels below 5 µg/l and three more with levels below 30 µg/l. Four sites with levels between 30 and 100 µg/l and one (Sabadell, Barcelona) with a level of 139 µg/l.

Chloroform accounts for over 90% of THMs in most waters; the exceptions being where bromide levels are high (Krasner *et al.*, 1989, Le Bel *et al.*, 1997, Cancho *et al.*, 1999).

Haloacetic acids (HAAs)

Haloacetic acid levels in potable water vary widely (similar to THMs) though they are usually somewhat lower. While there are WHO Guidelines (200 µg/l, 40 µg/l and 20 µg/l respectively for TCA, DCA and MCA), there are no EU limits.

Potable water surveys in Spain (Cancho *et al.*, 1999, Villanueva *et al.*, 2003) and Canada (LeBel *et al.*, 1997) found HAA levels between 30% and 70% of THM levels. Partly this reflects the fact that whilst THM levels normally increase in distribution systems, HAA levels may rise (but can also fall) in 'mature' water by hydrolysis and/ or biodegradation within the pipes. Most often, TCA and DCA levels are similar and MCA levels are almost always low.

HAA levels can be particularly high in chlorinated water derived from upland, acidic raw water sources partly due to the abundance of suitable precursors. In a survey of Finnish potable water, Nissinen *et al.* (2002) found HAA levels ranged from 6 µg/l to 255 µg/l in 24 surface water derived samples, whereas levels were undetectable in the four groundwater sources studied. Similarly, Graham *et al.* (2009) found HAA levels in the UK ranged up to 1.9 µg/l max (0.6 average) for a groundwater source, up to 20 µg/l max (11.9 average) for a lowland surface water and up to 41 µg/l max (21.3 µg/l average) for an upland surface water. Earlier studies in the UK found much higher levels; for example Hutchison *et al.* (1993) who found 147.8 µg/l DCA and TCA in water from an upland lake whilst Malliarou *et al.* (2005) found averages between 35.1 and 94.6 µg/l with a peak of 244 µg/l.

The 2010 HIWATE study of 11 EU locations (Jeong *et al.*, 2012) found HAA levels ranging from <1 to 51.5 µg/l, with an average of 15.9 µg/l. Four locations were <5 µg/l, a further five <30 µg/l and two >30 µg/l. In a 2010 study in Spain, Villanueva and Font-Ribera (2012) found median HAA levels in 217 samples from 11 provinces of 26.4 µg/l with a range between 0.9 and 86.9 µg/l.

Improved treatment techniques can markedly reduce HAA levels where these are high, with increased method adoption probably explaining the lower levels seen in more recent surveys. In the Nissinen *et al.* study (2002), waters prepared using such techniques had HAA levels between 6.4 and 36 µg/l whereas those without such improvements ranged from 36 to 255 µg/l. The Nissinen study also showed that whereas the HAA:THM ratio in most waters was 0.3:0.7, in upland acid waters where HAAs dominate, ratios between 1.5 and 67 were reported.

Halogenated aldehydes, ketones and acetonitriles

Though WHO drinking water guidelines for this group of substances are of the same order as THMs and HAAs (chloral hydrate 100 µg/l; dichloroacetonitrile 20 µg/l; dibromoacetonitrile 70 µg/l), actual reported levels are typically an order of magnitude lower.

The HIWATE study (Jeong *et al.*, 2012) thus found average levels for two haloketones of 1.87 µg/l (range <1 – 6.86 µg/l), four haloacetonitriles of 3.17 µg/l (Range <1 – 8.88 µg/l) and chloral hydrate (which is often regarded as the third most-prevalent DBP after the THMs and HAAs) averaging 3.3 µg/l (Range < 1 – 23.2 µg/l). Similarly, Villanueva *et al.* (2012) found 16 Spanish samples (analysed for haloacetonitriles, haloketones, chloropicrin and chloral hydrate) showing levels from <1 µg/l to 5.5 µg/l.

Halofuranones

Onstad *et al.* (2008) measured chlorinated and brominated forms of MX in the disinfected waters of six pairs of U.S. drinking water treatment plants. The maximum level noted was ~310 ng/l in finished water.

The 2010 Spanish survey by Villanueva *et al.* (2012) found MX levels in 36 samples with a median concentration of 16.7 ng/l (range 0.8-54.1 ng/l). Smith *et al.* (2015) collected 79 samples at consumers' taps in eight water supply zones in an extensive survey around Bradford, UK between 2007 and 2010. They found concentrations of MX varied between 8.9 and 45.5 ng/l with a median of 21.3 ng/l. MX also demonstrated clear seasonality with concentrations peaking in late summer/ early autumn. Multivariate regression showed that MX levels were associated with total trihalomethanes, UV-absorbance and pH.

Zheng *et al.* (2015), in bench experiments analysing MX and mucochloric acid (an open-ring furanone analogue) formation from three source waters in Ontario, Canada, found MX and mucochloric acid formation was 6.9-15.3 ng/l and 43.2-315 ng/l respectively. MX was the only measured DBP that contributed to genotoxicity, representing less than 0.001% of AOX by mass but responsible for 40-67% of the genotoxic response in the chlorinated water samples.

Inorganics

In Italy (where use of chlorine dioxide as a disinfectant is common), Aggazzotti *et al.* (2004) found trihalomethanes levels (THMs) were low (median: 1.10 µg /), whilst chlorite and chlorate concentrations were relatively high (chlorite median; 216.5 µg/l, chlorate median; 76.5 µg/l).

In Spain, Garcia-Villanova *et al.* (2010) found that two-thirds of the treated waters monitored had bromate concentrations higher than 1 µg/l, with a median value of 8 µg/l and a maximum of 49 µg/l. These concentrations were higher than those reported in other areas. Median values for chlorite were 5 µg/l, and 119 µg/l for chlorate.

Emerging disinfection by-products

In a survey of US drinking water treatment plants, Weinberg *et al.* (2002) typically found iodo-THMs at levels <1 µg/l, though in one plant, levels ranged between 0.2 and 15 µg/l. Richardson *et al.* (2008) found iodo-acids and iodo-THMs in waters from most US plants surveyed. The iodo-acids were present at levels up to 1.7 µg/l (iodoacetic acid) and the iodo-THMs at up to 10.2 µg/l (bromochloroiodomethane). Iodo-DBPs were highest in plants with short free chlorine contact times (<1 min), and were lowest in chlorine-only plants or in plants with long free-chlorine contact times (>45 min). Iodide levels in source waters ranged from 0.4 to 104.2 µg/l (when detected).

In the UK, Goslan *et al.* (2009) found iodo-THMs were at generally lower levels than reported in the US, <1 µg/l and of the order of 1% of total THMs.

Bond *et al.* (2011) collated data from surveys undertaken in the United States and calculated that the sum of analysed halonitromethanes represented 3-4% of the median mass of THMs.

Nitrosamines

Measurable nitrosamine formation is observed with chloramination disinfection processes, particularly when there is no pre-contact with Cl_2. Although levels of up to 100 ng/l have been reported, median levels from studies in the US and Canada ranged from <1 to 3.3 ng/l. Studies in the UK (Dillon *et al.*, 2008) found levels up to 5.8 ng/l, whilst Templeton and Chen (2010), surveying 5 water systems likely to have elevated nitrosamine levels because of source water or treatment characteristics, found the majority of samples contained no detectable NDMA or other nitrosamines. NDMA was barely measured above the detection limit of 0.9 ng/l (measured in only a few samples from one system). Dillon *et al.* (2012) however, identified water samples in certain treatment works up to 146 ng/l and concluded that the majority arose from contaminated ferric coagulants.

Fristachi and Rice (2007) assessed the proportion of total human exposure likely to be attributable to drinking water and concluded that, at a mean NDMA concentration of 2 ng/l, drinking water would contribute less than 3% of the total external exposure. The human body generates nitrosamines internally however, and when they took this into account the drinking water contribution to total exposure was less than 0.02%. Hrudey *et al.* (2013) updated this estimate using a revised approach regarding endogenous production and concluded that drinking water would contribute between 0.0002% and 0.001% for surface water systems using free chlorine or between 0.001% and 0.01% for surface water systems using chloramines.

4.2 Pools

The majority of swimming pools use variations of active chlorine to provide the constant disinfectant residual necessary to keep them biologically safe for use. The DBPs produced consist of the same families that are formed in potable water and whilst the patterns are similar, levels are generally rather higher. HAAs tend to be present at greater levels than THMs, with most other DBP families at an order of magnitude or more lower concentration. Outdoor pools tend to have higher levels of non-volatile DBPs, as higher disinfectant doses are often used to maintain the residual in open, well-lit conditions. Although more than 600 individual DBPs have been identified in pools (Richardson *et al.*, 2010), the proportion of unidentified organic halogens, likely to be sparsely chlorinated natural organic matter, tends to be lower especially where DBP levels are higher as reactions go to completion and DCA and TCA predominate.

Pool studies over the years have reported DBP levels that vary much more widely than for potable water, with many such studies being summarised in work by Teo *et al.* (2015). Rather than input water quality, the main determinants of DBP levels in pools are good pool management and user behaviour (e.g. hygiene). This is because most DBPs form from reactions with urine, sweat and other substances on the user's skin (e.g. cosmetics). Where possible, levels quoted below are chosen to reflect typical pools rather than badly managed or 'misused' ones.

Trihalomethanes (THMs)

THM levels can reach around 200 µg/l, but mean levels are commonly below 100 µg/l which is the permitted EU drinking water level (Sodium Hypochlorite Risk Assessment Report (RAR), 2007, Font-Ribera *et al.*, 2010, Simard *et al.*, 2013). Around 90% of the THM present is chloroform, other than in high bromide waters or when active bromine is the disinfectant in which case bromoform predominates (Sodium Hypochlorite RAR, 2007, Teo *et al.*, 2015).

Haloacetic acids (HAAs)

Being polar and non-volatile, haloacetic acids tend to build to higher levels in pools than THMs. Total HAA levels can range between 500 and 1000 µg/l, but mean levels are typically well below 500 µg/l. Tri- and di-chloroacetic acids dominate, accounting for 93% of all HAAs in a survey of 54 pools in Quebec City, Canada (Simard *et al.*, 2013). Again, brominated derivatives can predominate in high bromine conditions.

Other organohalogens

Trichloracetaldehyde (chloral hydrate) is the main haloaldehyde in pools and often approaches levels similar to the THMs (Sodium Hypochlorite RAR, 2007, Lee *et al.*, 2010). These are now quantifiable after Serrano *et al.* (2014) reported the development of an analytical method and first quantification of haloketones in swimming pools.

The pattern for haloacetonitriles in pools appears to parallel that in drinking water; levels are typically an order of magnitude lower than THMs/ HAAs with dichloroacetonitrile being the dominant DBP (Teo *et al.*, 2015). Weaver *et al.* (2009) measured cyanogen chloride and bromide in eleven pools ranging from 1-10 µg/l. Halonitromethanes have been measured at levels of the order of 1 µg/l (Teo *et al.*, 2015).

Chloramines

Chloramines have traditionally been collectively measured in pools and potable water as 'combined chlorine' using the DPD (N,N diethyl-1,4 phenylenediamine sulfate) method. Combined available chlorine functions as a disinfectant similar to, though less effective than, free available chlorine with monochloramine being employed in such a role. Weaver *et al.* (2009) however used membrane-introduction mass spectrometry (MIMS) to measure individual inorganic chloramines. They most often found chloramine concentrations between 0.1 and 0.5 mg/l (monochloramine invariably predominating), but with wide variation in individual chloramines.

Jacobs *et al.* (2007) measured volatile chloramines in the air above six Dutch swimming pools and found levels ranged between 0.13 and 1.34 mg/m^3 with an average of 0.56 mg/m^3. They developed a model to predict long-term levels according to various influencing factors with, in addition to the free chlorine concentration in the pool water, the model indicating an increase of 0.4 mg/m^3 in air concentration of chloramines with every 50 additional bathers. A later study (Jacobs *et al.*, 2012) found lower trichloramine levels, averaging 0.21 mg/m^3.

In this study the highest measured value was 0.78 mg/m^3 and the highest daily average level was 0.44 mg/m^3. About 90% of the levels were below the WHO guideline of 0.5 mg/m^3.

4.3 Cleaning

The range of DBPs formed when bleach is used in domestic cleaning procedures, and to which people may be exposed, again parallels those formed in potable water; although concentrations in cleaning solutions are sometimes much higher (TNO Delft, 1991, Smith, 1994, AISE, 1997, Sodium Hypochlorite RAR, 2007). Formation of DBPs from household use of bleach has been studied at a 'community' level (i.e. in a group of apartment blocks in Italy; Schowanek *et al.*, 1996) as well as for individual processes; most notably laundry (Smith, 1994) and floor cleaning (Josa and Osset, 1997). Laundry is observed to result in greater levels of DBP formation than in floor and toilet cleaning because of the higher levels of organic substrates present and the higher temperatures. For example, Smith (1994) found 2.6% of the applied chlorine was converted to organically-bound halogens, measuring average levels of 535 µg/l for chloroform and around 1000 µg/l for haloacetic acids. Dichloroacetonitrile was, as for potable water, an order of magnitude lower.

Josa and Osset (1997) found overall DBP formation rates in toilet (0.06%) and floor cleaning (0.12%) solutions much lower, but with higher applied doses and lower 'soiling' levels. THM and HAA levels in cleaning solutions for these applications are expected to be of the same order (~100 µg/l) as typical regulatory limits for potable water (Peeters, 1991).

Although there are substantial flows of polyhalogenated dioxins and furans in domestic wastewater, extensive studies by Horstmann, McLachlan and co-workers established that this does not arise from bleach use (and it would not be expected as usage occurs at circum-neutral or alkaline pH) but primarily from the laundering of contaminated textiles (Horstmann *et al.*, 1992, 1993a, 1993b, Horstmann and McLachlan 1994a, 1994b, 1995a, 1995b, 1995c).

In formulated bleach solutions there is a small conversion of hypochlorite to chlorate and chloride, with 10 to 20% of the hypochlorite being broken down in domestic products after storage for 1 year at 20°C.

4.4 Comparable human exposures from 'other' household water uses and swimming pools.

The focus of regulation and guidelines designed to control exposure to DBPs has been primarily on potable tap water supplies and, to a lesser extent, on swimming pools. The standard assumption in health risk assessment and exposure calculations of potable water is that a person drinks approximately 2 litres of water per day. More recently though, studies have shown how exposure to DBPs from potable water arises not only from ingestion, but from a range of different household activities which use water.

The most significant of these 'alternative' activities is showering and bathing, particularly for volatile DBPs (such as those THMs which can be inhaled), as evaporation rates are greater from hot water. The results described below are illustrative of the findings of numerous different studies on water usage of this type.

Trihalomethanes (THMs)

Xu *et al.* (2002) studied permeation rates through the skin for THMs and calculated that a weekly pattern of around five 7-minute showers and one 12-minute bath would result in a daily internal dose through dermal adsorption of approximately 40-70% of the daily ingestion dose. Xu and Weisel (2005) studied chloroform levels in air and exhaled breath of six volunteers in a controlled showering experiment. They measured a mean air chloroform concentration in the shower stall of approximately 180 µg/m^3 from water containing 18 µg/l of chloroform. From exhaled breath and other measurements they concluded that inhalation exposure to chloroform from water during a 10-15 minute shower was equivalent to drinking 0.5 – 1.4 litres of that water. In a subsequent larger study with 100 volunteers at two sites (Silva 2013), a median THM concentration in water of 96.4 µg/l gave a median shower air concentration of 351 µg/m^3 respectively compared to a baseline air concentration of 5.8 µg/m^3. These findings are broadly in agreement with previous studies by May *et al.* (1995), Kerger *et al.* (2000) and Egorov *et al.* (2003).

Two related studies in the USA (Nuckols *et al.*, 2005, Gordon *et al.*, 2006) examined a range of household water-using activities. In the former study, showering gave the highest median air THM concentrations of the various activities; 95 and 384 µg/l respectively at two sites where THM concentrations in the water were 41 and 187 µg/l. In the latter, showering again gave the highest air concentrations relative to the water levels (2.3 µg/m^3 per µg/l in water) followed by bathing (0.7 µg/m^3 per µg/l).

Several household cleaning activities were also studied. The following table (Table 2) shows levels measured by Gordon *et al.* (2006) in air, and in exhaled breath relative to the level in the water supply.

Table 2 Relative THM exposure values for various (non-drinking) potable water activities.

	Relative THM concentration (µg/m^3 per µg/l in water)	
Activity	Air	Exhaled breath
Hot shower	2.3	0.19
Hot bath	0.7	0.25
Preparing hot drink	0.1	0.04 (after drinking)
Washing hands	0.2	0.03
Machine clothes washing	0.15	0.06
Machine clothes washing with bleach	0.3	0.12
After auto dishwashing	0.3	0.075
Hand dishwashing	0.25	0.13

Smith (1994) found that shower cleaning with a bleach-based cleaner could generate similar levels in air to machine laundry with bleach.

Concentrations of THMs in swimming pool water and air have been extensively investigated, and several studies have measured THMs in exhaled breath. Results as summarised by Lourencetti *et al.* (2012) (who also reported their own measurements) differentiated between swimmers, bathers (instructed not to exercise) and bystanders (not in the pool). Mean THM levels in water in the various studies ranged up to 120 µg/l, although levels of 30-50 µg/l were most common. Mean THM levels in air ranged similarly up to around 230 µg/m^3, although air levels relative to water were more variable due (most likely) to differences in ventilation etc. Exhaled air levels in swimmers reported by Lourencetti *et al.* (2012) averaged around 7-8 µg/m^3, compared to half that level for non-exercising bathers. Mean THM levels in water were 49 µg/l and in air, 72 µg/m^3. Expressed as µg/m^3 per µg/l in the water yielded ratios of around 1.5 for air and 0.16 for breath which are towards the higher end of the exposure ratios observed by Gordon *et al.* (2006) for domestic water-using activities (based on table 2 above).

Haloacetic Acids

Xu *et al.* (2002) found permeation rates of HAAs through skin to be minimal, as would be expected given their polar nature, deducing that dermal absorption from showering and bathing would add <0.1% to the daily ingested dose. Xu and Weisel (2003) measured airborne concentrations of HAAs in particulates and aerosols in showers. Since little would be present in the vapour phase, they concluded that inhalation would similarly add insignificantly (<0.5%) to the ingested dose.

Because HAAs are neither volatile nor dermally absorbed, no significant addition to the dose from drinking water would be expected from cleaning tasks. Concentrations in swimming pools however can be substantially higher than in drinking water. The potential for uptake through skin or inhalation remains low but ingestion of significant quantities (e.g. by children) could contribute significantly to daily dose.

Other halogenated organics

Relative exposures to other DBPs across different activities are expected to fall between the patterns for THMs (for volatile DBPs) and for HAAs (for non-volatile, polar species considering water concentrations will be one or more orders of magnitude lower). For example, Xu and Weisel (2005) found that although haloketones are volatile, only 10% of the water content was released to air compared to 56% for chloroform. Haloketone dermal dose was estimated to be around 10% of the ingestion dose, falling between THMs (40-70%) and HAAs. Trabaris *et al.* (2012) found that the permeation of haloacetonitriles was substantial, such that monthly dermal doses for swimmers could be 40-75% of a typical ingested dose. Chloral hydrate, an important DBP in pools however, showed much lower permeability such that the dermal dose would be around 2% of the dose from drinking water.

The studies summarised above show that exposures from activities such as showering, bathing and swimming, and to a lesser extent from cleaning tasks, can cause significant exposures to DBPs, especially volatile ones such as THMs. However, the actual pattern of exposure for a given individual will vary according to the nature and duration of their activities. Font-Ribera *et al.* (2009), for example, studied the different patterns among 2000 children aged between 9 and 12 in Sabadell, Catalonia, Spain where 80% of the children drank bottled water and 20% regularly attended pools. In this study, whilst showering was the most important exposure for non-swimmers, pools were the most important source for regular swimmers.

In summary, from a risk assessment perspective, domestic cleaning exposures are generally less than those from drinking 2 litres of the relevant tap water on which risk assessment is conventionally based. Similarly, exposures from swimming in pools that are well-managed and responsibly used will be a fraction of the exposure from ingesting 2 litres of tap water with the maximum allowed concentrations of THMs (100 µg/l in Europe).

5. Epidemiological evidence relating to possible adverse effects from different uses

5.1 Drinking Water

Over the four decades since the discovery of DBPs in drinking water, many epidemiological studies of increasing power and sophistication have been performed in relation to possible increased risks of adverse health effects. The two main foci for these studies have been on cancer and reproductive effects (based on the hazards and suspected risks initially associated with major DBP families such as the THMs and HAAs). The evidence from such studies has been reviewed by various authors, most notably in an assessment by IPCS (2000), by Nieuwenhuijsen *et al.* (2009a) and more recently by Villanueva *et al.* (2015).

Cancer

IPCS noted positive associations between various metrics of exposure to chlorinated drinking water and bladder and colorectal cancer but also noted conflicting results. The authors highlighted shortcomings in the design of many studies, particularly early ones, leading to probable bias. They noted this was in addition to the inadequacy of exposure measures which were often geared towards major DBP families and focused on ingestion rather than the wider range of routes of exposure now seen as relevant to some DBPs (including inhalation and dermal routes). They noted that a controversial meta-analysis study (Morris *et al.*, 1992) combining the results of 10 earlier studies showed a small-pooled relative-risk for bladder and rectal cancer but not colon cancer but "included a number of low-quality studies with likely bias". They cited a formal evaluation of the meta-analysis by Poole (1997) which concluded that such studies should not have been combined into aggregate estimates of relative risk or used as the basis for national attributable risk estimates.

IPCS concluded that "current evidence from epidemiological studies is insufficient to allow a causal relationship between the use of chlorinated drinking water and the incidence of bladder cancer to be established. Several studies reported weak to moderate associations of long-duration exposure to chlorinated water and bladder cancer, but risks have differed between smokers and non-smokers in several studies. Inconsistent risks have also been seen when gender and water consumption were considered. For colon cancer, the epidemiological data appear to be equivocal and inconclusive. For rectal cancer, insufficient data are available with which to evaluate the moderate associations observed in one study. Similarly, single studies of reported associations for pancreatic, lung, brain and breast provide insufficient data."

A UK government scientific advisory committee on carcinogenicity (COC[1], 2008) reviewed the available evidence in 2007. They concluded that "the evidence for a causal association between cancer and exposure to chlorination by-products (CBPs) is limited and any such association is unlikely to be strong". They considered that recent data provided limited evidence for an association between bladder cancer and exposure to CBPs in men, but that the evidence in women was conflicting.

Nieuwenhuijsen *et al.* (2009a) considered that there "appeared to be good epidemiological evidence for a relationship between exposure to DBPs, as measured by THMs, in drinking water and bladder cancer, but that the evidence for other cancers including colorectal cancer [was] inconclusive and inconsistent."

[1] Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Further, a pooled analysis by Villanueva *et al.* (2004) found an exposure-response relationship between THM intake and bladder cancer for men, but no relationship for women. A case-control study in Spain (Villanueva *et al.*, 2007), taking into account exposure through showering and bathing, found significant associations between projected THM exposure based on retrospectively reported habits and assumed historical levels and bladder cancer, but the increase in odds ratios in relation to estimated ingestion alone was not significant.

Cantor *et al.* (2010), working with cases from the above study, found that the association between projected THM exposure and bladder cancer was significant and stronger for the two more exposed quartiles in cases with certain polymorphisms of three genes; whereas the association was significant only for an intermediate quartile across the whole population. The authors note evidence for the involvement of the genes in metabolism of brominated THMs, haloacids and halogenated hydrocarbons respectively.

Costet *et al.* (2012) then conducted a further pooled analysis of three case-control studies from France, Finland and Spain. Projected exposure to DBPs based on estimated Total THM levels and personal water consumption was associated with bladder cancer risk for men (OR1.47; 1.05 – 2.05 for average total THM >50 µg/l vs. ≤5 µg/l) but also, not for women. The authors commented that the associations were similar for European and US populations despite differing water disinfection practices.

The evidence regarding bladder cancer was reviewed again by Hrudey *et al.* (2015) who summarised the strengths and weaknesses of those available studies. They highlighted concerns with exposure measurements, particularly with extrapolating back in time based on recent measurements. DBP levels were likely to have been higher before attempts to control them began and increased risks detected may thus be due to much greater exposures than indicated by the studies. Hrudey *et al.* (2015) noted interesting findings suggesting greater susceptibility among those with specific genotypes, but stressed the importance of replicating these findings in different settings and populations.

Hrudey *et al.* (2015) also comment that summing all the available cancer risk estimates for DBPs would not yield a risk as great as that suggested by studies solely for THMs. Therefore, if the observed increased risks are ultimately shown to be caused by DBPs, this would suggest that the responsible agent(s) have not yet been identified. Accordingly they caution against further tightening of DBP limits in the USA until there is clearer evidence to justify and to target such a step where it would likely to be effective.

As regards colorectal cancer, Kuo *et al.* (2009; in a matched case-control study of all colon cancer deaths between 1997 and 2006 in 65 municipalities in Taiwan) found no significant association between total THM levels in drinking water and risk of death from colon cancer. A meta-analysis of 13 studies was performed by Rahman *et al.* (2010). On their selection of 13 studies (10 case-control, 2 retrospective cohort and one prospective cohort) they found "limited evidence of a positive association between colorectal cancer and exposure to DBPs in drinking water" but commented that causal inference was not possible.

Finally, Rahman *et al.* (2014), using a five year lag of exposure found a positive association between bromoform concentration and colorectal cancer in men (IRR = 1.025, 95% CI 1.010, 1.040) but not in women (IRR = 1.003, 95% CI 0.987, 1.018). The association in men was mainly found in colon cancer linked with bromoform (IRR = 1.035, 95% CI 1.017, 1.053). No appreciable association of colorectal cancer was noted with other species of THMs in the Rahman *et al.* (2014) study.

Reproductive Effects

The IPCS review (2000) considered that existing epidemiological data at that time were insufficient to allow the importance of the observed associations of chlorinated drinking-water/ THMs and adverse pregnancy outcomes to be assessed. They commented that although several studies suggested that increased risks of neural tube defects and miscarriage may be associated with THMs or selected THM species, additional studies were needed to determine whether the observed associations were correct or not.

Numerous further studies have since been conducted. Reviewing the evidence in 2009(a), a Nieuwenhuijsen *et al.* study concluded "there appears to be some evidence for an association between exposure to DBPs, specifically THMs, and little for gestational age/ intrauterine growth retardation and, to a lesser extent, pre-term delivery, but evidence for relationships with other outcomes such as low birth weight (LBW), stillbirth, congenital anomalies and semen quality is inconclusive and inconsistent. Major limitations in exposure assessment, small sample sizes and potential biases may account for the inconclusive and inconsistent results in epidemiological studies". The authors further commented that although several mechanisms for such effects have been suggested they had not been well investigated.

Subsequent studies on aspects such as foetal growth and pre-term birth have found little evidence for effects when focusing on THMs. For example, in a systematic review and meta-analysis by Grellier *et al.* (2010), "little or no evidence for associations between total trihalomethane concentration and adverse birth outcomes relating to foetal growth and prematurity, with the possible exception of small for gestational age [SGA]" was found.

Patelarou *et al.* (2011) found no evidence of increased risk of LBW, SGA and pre-term delivery at relatively low level exposures to THMs and (particularly) brominated THMs in a Cretan drinking water. Villanueva *et al.* (2011), despite high THM levels in some areas in their study in Spain, and an extensive exposure assessment, found results suggested that residential THM exposure during pregnancy, driven by inhalation and dermal contact routes, is not associated with birth weight, SGA, LBW, or pre-term delivery.

Results from studies looking at a wider range of DBPs are more variable. A study of pre-term birth (Aggazzotti *et al.*, 2004) showed no association with DBP exposure; whilst term-SGA (small for gestational age), when chlorite levels are ≥200 µg/l combined with low and high levels of inhalation exposure are considered, suggested a dose-response relationship (adjusted-Odds Ratios (ORs): 1.52, 95%CI: 0.91-2.54 and 1.70, 95%CI: 0.97-3.0, respectively).

However, the results of Horton *et al.* (2011) did not support an association between total THMs or HAA and SGA birth, pre-term birth (PTB), or very PTB (<32 weeks' gestation), but they did report an association between increased TOX load and PTB.

Interestingly, Zhou *et al.* (2012), using urinary creatinine ('Cr') adjusted TCA as an exposure biomarker, found no statically significant results in linear regression analysis but commented that for both the crude and adjusted results, the mean birth weight of the subjects in their third and top quartiles of Cr-adjusted urinary TCA concentrations was decreased when compared with those in the lowest quartile.

Costet *et al.* (2012), studying the PELAGIE cohort (a French birth cohort comprising 3,421 pregnant women recruited between 2002 and 2006), found that higher uptake of THMs (especially brominated THMs) was associated with a higher risk of foetal growth restriction (FGR). Women with TCA detected in their urine (>0.01 mg/l) had a higher, but not statistically significant, risk of FGR than those with TCA levels below the detection limit and had an odds ratio for preterm birth below 1. Rivera-Nunez and Wright (2013) detected consistent associations between adjusted mean BWT (birth weight) and brominated THM (THMBr) exposures.

In a Canadian study, Ileka-Priouzeau *et al.* (2015) found SGA status in newborns was not associated with exposure to low levels of HAAs and haloacetonitriles (HANs) through drinking water during the third trimester of pregnancy.

Turning to other reproduction-related adverse effects, Iszatt *et al.* (2014), studied DBPs in public water supplies and semen quality, finding that concentrations of THMs were not associated with poor semen quality.

Hwang and Jaakkola (2012) compared the risk of stillbirth in four disinfection by-product exposure categories based on the levels of total trihalomethanes. They then conducted a meta-analysis of the results from this and 5 previous studies focusing on stillbirth. The authors reported that in the meta-analysis, the summary odds ratio for stillbirth (1.11, 95% CI: 1.03, 1.19) was consistently elevated.

Despite these studies, Nieuwenhuijsen *et al.* (2009b) found during meta-analyses of all currently available studies relevant to a potential association between chlorination by-products and congenital anomalies, little evidence of such an association.

In a novel study, Iszatt *et al.* (2014) examined stillbirth and low birth weight rates before and after an intervention in 2003-4 to introduce enhanced coagulation at 4 large drinking water treatment works in northern England to reduce THM levels. The authors concluded that overall, the change was not associated with a statistically significant reduction in birth outcome rate and that there were no significant decreases in stillbirth rates. However, areas with the highest chloroform decrease (30 - 65 µg/l) had the greatest percentage decrease in low -9 % (-12, -5) and very low birth weight -16% (-24, -8) rates, but only the latter was statistically significant.

A study by Righi *et al.* (2012) highlighted the potential for increased risks of DBPs from alternative disinfectants. Chlorine dioxide, which is extensively used in Italy, particularly in larger works, forms both chlorite and chlorate by-products.

In summary, evidence of an association between exposure to DBPs and adverse health effects seems most consistent for bladder cancer, although the causal nature of the association remains inconclusive (Villanueva *et al.* 2015). These authors further summarise how evidence concerning other cancer sites is “insufficient or mixed”. Studies looking for associations between THMs in general and adverse reproductive outcomes have mainly negative findings, although some associations have been found in more recent studies focusing on brominated species and other DBPs such as haloacetic acids. Villanueva *et al.* (2015) comment that “the body of evidence suggests only minor effects from high exposure during pregnancy on foetal growth indices such as SGA at birth”.

5.2 Pools

Exposure to DBPs arising from swimming in pools has only occasionally been studied in isolation but, like showering and bathing, has become more frequently assessed in epidemiological studies of possible increased risks of cancer or reproductive problems. Here, findings are generally similar to those for potable water.

Pools however, unlike drinking water, produce exposure to volatile respiratory irritants, notably trichloramine formed by reaction with (amino-)nitrogen primarily introduced by users as natural body oils, sweat, urine etc. It should be remembered though that trichloramine levels should be modest in properly managed and used pools.

Massin *et al.* (1998) reported an exposure-response relationship between airborne chloramines and symptoms of eye, nose and throat irritation in workers at swimming pools (but not for chronic respiratory symptoms or bronchial hyper-responsiveness). Trichloramine has also been proposed as a potential cause of occupational asthma in pool workers (Thickett *et al.*, 2002) based on three case reports. Jacobs *et al.* (2007) found pool workers in The Netherlands showed increased general respiratory symptoms, finding the frequency of upper respiratory symptoms was related to exposure to chloramines at the pools, whilst lifetime or physician-diagnosed asthma was not.

Interestingly, the prevalence of asthma and bronchial hyper-responsiveness is higher in athletes, especially in endurance sports (Carlsen, 2009). However, several studies have reported increased respiratory symptoms, including asthma, amongst adult elite swimmers compared to other athletes; though it is uncertain why as Pedersen *et al.* (2009) found no evidence of airway damage in adolescent elite swimmers. In a meta-analysis of six such studies Goodman and Hays (2008) found a meta-odds ratio between 2.3 and 2.6 but cautioned that the direction of causation is not known, particularly as asthmatics are encouraged to choose swimming as a 'less-asthmagenic' form of exercise by specialists.

Reviewing the evidence in 2015, Villanueva *et al.* commented that "populations highly exposed to swimming pools, such as pool workers and professional swimmers show a higher prevalence of respiratory symptoms and asthma, respectively, although the direction of the association, and thus causality, is not clear among professional swimmers".

A series of studies in Belgium, beginning in 2003, hypothesised that children, particularly those who swam as babies or infants, can suffer damage to the lung epithelium from chloramines. It was suggested that this may lead to asthma, and further, could partly explain the sharp rise in asthma in recent decades (Bernard and Nickmilder, 2006, Bernard *et al.*, 2003, 2006, 2008, 2009). Most of these studies were conducted on some hundreds of children over 10 particular schools.

Together, these studies report numerous positive associations between respiratory end-points and increased exposure to swimming pools, though often for particular sub-sets of the study population. In an initial study (Bernard *et al.*, 2003), a positive association was reported between cumulative pool attendance (as indicated by questionnaire) and the use of asthma medication or exercise-induced bronchospasm (EIB). A subsequent study (Bernard and Nickmilder, 2006) found cumulative pool attendance was significantly associated with chest tightness and coughing, and with exhaled NO (nitrogen monoxide, an indicator of eosinophilic airway inflammation) but associations with doctor-diagnosed asthma and EIB remained non-significant. A parallel study by the same group (Bernard *et al.*, 2006) found baby swimming significantly associated with EIB, chest tightness and recurrent bronchitis. Later, Bernard *et al.*, (2008) found significant positive associations between outdoor swimming and doctor-diagnosed asthma, but no significant association with attendance at indoor pools except for the most frequent indoor-oriented swimmers. A subsequent analysis (Bernard *et al.*, 2009) found a positive association between cumulative overall pool attendance and asthma, but not with EIB. A follow-up study (Voisin *et al.*, 2013a, 2013b) found less asthma in early swimmers. These studies also reported significant specific associations or interactions involving atopic status.

There have also been positive findings in studies from other countries, for example an association between number of years swimming and wheezing and diagnosed asthma in a small study of boys in Ireland (Cotter and Ryan 2009). A questionnaire-based study on a large birth cohort in Norway (Nystad *et al.*, 2008) also found some associations between respiratory function and swimming at 6 months. Wheezing and the specified infections were no more common among the 25% of babies who went swimming, though there was an increased risk of wheeze (OR 1.24 [95% CI] 1.11, 1.39) amongst swimming babies who had atopic mothers. Children without respiratory diseases before 6 months of age had an increased risk of wheeze (aOR 1.08 (1.02–1.15)), if they took part in baby swimming.

However, studies in other countries, including Canada (Levesque *et al.*, 2006), Italy (Carraro *et al.*, 2006), Germany (Kohlhammer *et al.*, 2006), Spain (Font-Ribera *et al.* 2009), the Netherlands (Jacobs 2012) and the UK (Font-Ribera *et al.*, 2010) have failed to find significant positive associations between swimming and asthma in children. In contrast with other studies, most of these studies each comprised of several thousand children. The UK study is seen as particularly significant as this was the first large, longitudinal prospective study, on some 5,700 children. It assessed children and their lifestyles seven times between age 6 months and 7 years but found no association between swimming and asthma during that period. Further, it found that children who swam had improved lung functioning and indeed, those with previous respiratory conditions were less likely to have asthma at the time of assessment.

Goodman and Hays (2008) conducted a meta-analysis of those studies available at the time and concluded that "there appears to be no consistent association between the prevalence of asthma and swimming pool use during childhood". Reviewing studies available some years later, Villanueva and Font-Ribera (2012) concluded that "most of the scientific evidence does not support the hypothesis that recreational swimming increases the risk of childhood asthma".

Since most of the studies suggesting increased risks of asthma concerned Belgium, the issue was reviewed by the Belgian Superior Health Council in 2011. They concluded that swimming remains highly advisable, even for those with asthma as "the advantages of swimming under good hygienic conditions in monitored pools outweigh the risk of toxicity related to chlorine and its by-products". In a follow-up report in 2012 (Belgian Superior Health Council, 2012) considering the advisability of baby-swimming, the Council confirmed that it did not advocate this, citing both a lack of clear benefit and the particular vulnerability of babies such as to infections and other microbial hazards. It also re-confirmed its opinion advocating swimming for other (older) children.

In a further review of the literature, Heederik *et al.* (Pers. Comm.) arrived at similar conclusions stating "the indications for associations between swimming exposure, atopy and asthma are at best inconsistent but not very strong". They considered a 20 paper meta-analysis unfeasible because of the heterogeneity of, and weaknesses in the various study designs. They did however consider and comment on possible reasons why the studies in Belgian schools tended to yield indications of increased risk (albeit varying from study to study) where other studies found no evidence of increased risk. A plausible suggestion was that taking samples from specific schools, which have different characteristics in terms of (e.g.) socioeconomic parameters, may have contributed to an 'ecological fallacy' which may have led to a systematic bias.

5.3 Cleaning

Exposure to DBPs can occur during cleaning, simply from the water used. This applies especially to volatile DBPs in situations where hot water is used (e.g. in hand-dishwashing). Even where bleach is used in cleaning, exposure to DBPs will, as noted above, be a fraction of that arising from potable water at the (legal) safe limits.

It has been observed from many studies that people working professionally as cleaners are about twice as likely as office workers to suffer (for example) from asthma or similar respiratory problems. It is unclear whether the issue is primarily one of increased symptoms, or due to their exacerbation in people with pre-existing respiratory problems, or to what extent there is increased onset among cleaners. It is similarly unclear as to what extent the increased risk arises from cleaning products, or from substances or microbes in the area being cleaned, or is associated with other factors in the broader lifestyles of those who work as cleaners. To the extent that cleaning products may be a factor, it is not clear as to what extent increased risk may arise from proper use as per instructions as opposed to misuse or accidents.

A few studies exploring this question have identified bleach by-products as a possible source of irritants (chloramines) which might affect respiratory function. Cleaning with bleach can, in some circumstances, release trichloramine into the air in those areas where the area being cleaned has substantial levels of amino-nitrogen present. Because mixing bleach with products containing substantial quantities of acids or ammonia can release chlorine gas or trichloramine respectively, bleach products carry mandatory warnings *not* to mix with other products. These warnings are better observed in some countries than others, and accidental mixing may also occur.

In a study of professional domestic-cleaning personnel in Spain, Medina-Ramon *et al*. (2005) found that those suffering from asthma or bronchitis symptoms reported using bleach more often than those in control groups. They also recorded measurements for chlorine in the air which could only arise from mixing with acid products *unless* the measuring equipment was responding unintentionally to another agent (such as trichloramine). More than 50% of the participants reported past accidents involving inhalation of fumes and that was more common in cases than controls. Two thirds of these accidents involved product mixing. A quarter of participants reported mixing bleach into detergent-containing water for hand-dishwashing.

A subsequent study from the same group (Medina-Ramon *et al.*, 2006) examined short-term responses to the use of 'irritant' cleaning products, including bleach, which they concluded aggravated lower respiratory tract symptoms. Macãira *et al*. (2007) found that bleach and dust were the most commonly reported triggers for asthma and rhinitis symptoms in cleaning workers in São Paulo, Brazil.

Zock *et al*. (2009) analysed data from ECHRS, a 'large' longitudinal European study of the general public. They found elevated odds ratios for lower respiratory tract symptoms among people who reported using bleach at home more than 4 days/week compared to those who used no bleach at all. Less frequent use of bleach showed no significant increased risk. Conversely, in many countries of Europe (but not all) data showed a reduced likelihood of being atopic. However, the study did not consider what tasks the bleach was used for or the duration of use, both of which would be expected to markedly affect exposure and thus any health effect.

Whilst it might be expected that irritant vapours that can be evolved when bleach is used in certain ways might affect the symptoms of existing sufferers of respiratory disease (similar for many other irritants) the extent to which any new condition may be created, and whether that arises from normal use, or from misuse or accidents, remains unclear.

6. Conclusions

Much has been learned over the last 40 years about the formation of small (but potentially significant quantities of) halogenated organic by-products when active chlorine solutions are used to disinfect tap water, swimming pool water and areas being cleaned of harmful microbes.

Though the range of these disinfection by-products formed is wide, with several hundred different substances currently identified, the total concentration of these in tap water is generally less than 1 mg/l (sometimes a little higher in swimming pools).

Trihalomethanes and haloacetic acids dominate, and may sometimes account for more than half the total by-product composition. A 'second tier' of by-products, comprising haloacetonitriles, haloaldehydes, haloketones and halophenols are commonly present, but at an order of magnitude lower concentration. Chlorinated species dominate except where bromide levels are high in the water being treated.

New substances, collectively referred to as 'emerging' DBPs, are constantly being identified, but they are present at orders of magnitude lower concentrations still. It is often said that half or more of the halogenated organic species in tap water, pools or cleaning solutions remains 'unidentified'. However, the great majority of these are likely to be sparsely-halogenated organic macromolecules, such as humic and fulvic acids derived from decomposed vegetation, which can be present in the raw water. Such macromolecules are highly complex and difficult to 'speciate', even in their natural state.

Various families of these DBPs have hazards that could potentially harm health when present in sufficient doses. There are numerous *possible* carcinogens, including the THMs, but none of them are yet *confirmed* to cause cancer in humans. Some families, notably the haloacetic acids, have exhibited potential for reproductive or developmental toxicity.

A strong driver for the efforts to identify increasing numbers of 'emerging' DBPs is a concern that bacterial mutagenicity exhibited by DBP mixtures cannot be reconciled with known carcinogenic potential. Whilst it may be that there are, as yet undiscovered, potent carcinogens in the DBP mix (most likely present at very low concentrations) it may also be that mutagenicity tests are being 'over-interpreted'. Any sparsely-halogenated natural macromolecules making up the bulk of the unidentified halogenated organics are unlikely to be biologically active because of their relatively large molecular size.

As regards other hazards, volatile chloramines are strong respiratory irritants that could potentially impact respiratory health through their inhalation from the air above swimming pools, or in certain cleaning scenarios (including misuse and accidents).

Human exposure to DBPs depends on concentrations in the various media relevant to the route of uptake and the duration of exposure. Levels of THMs in EU potable water are limited by regulation to 100 µg/l but most supplies have now been brought below this level. Some, especially those EU supplies derived from groundwater (more than 50%), may be 10 times lower. Haloacetic acid levels are generally somewhat lower than THM levels, though they may be several times higher in supplies derived from upland, acidic 'peaty' waters. Other halogenated DBPs are generally at concentrations an order of magnitude or more *lower* than THMs and HAAs. Levels of the potent mutagen MX are of the order of 0.01 – 0.05 µg/l and nitrosamines around 0.002 µg/l.

Total halogenated DBP concentrations in swimming pools may be up to several times higher than in potable water, especially for haloacetic acids and chloral hydrate. As well as DBP in the input water source, levels depend *critically* on good pool management and user behaviour. Inorganic chloramines in pool water are typically of the order of 0.1 – 0.5 mg/l, dominated by the least volatile DBPs (monochloramine), whilst levels in air above indoor pools in a recent Dutch study were mainly below the WHO guideline of 0.5 mg/m^3.

Studies looking at the exposure arising from these levels have identified that domestic activities using water can also make an important contribution. For the THMs (which are volatile), hot-water uses such as showering and bathing have been estimated to add 40 – 70% to that of the exposure from drinking 2l of the water. Showers produced a higher in air concentration but bathing gave the higher exhaled breath concentrations per unit in water concentration itself. Comparatively, hand dish-washing gives about half this exposure, and hand washing about one tenth. Machine laundry using bleach gave an exposure similar to hand washing dishes (without bleach).

Studies of exhaled breath THM measurements among pool users showed, as would be expected, higher levels in swimmers than in bathers who were instructed not to swim; levels amongst people who stayed on the side of the pool were lower still. Broadly speaking, exposure as indicated by exhaled breath levels was similar per mg/l of THM in the water to domestic exposures.

Exposure from other water uses (including swimming) for haloacetic acids is low compared to that from ingestion of drinking water because of their polar, non-volatile nature meaning that neither inhalation nor dermal uptake is significant. Uptake of other halogenated organics sits between THMs and HAAs depending on polarity and volatility.

From a risk assessment perspective, domestic DBP exposures are thus generally *less* than the exposure from drinking 2 litres of the relevant tap water. Though exposures from swimming in pools can be the most important contribution to exposure for swimmers living where potable water DBP levels are low, the exposure from pools that are well-managed and responsibly used will similarly be a fraction of the exposure from ingesting 2 litres of tap water with maximum allowed concentrations of THMs.

The evidence from the many epidemiological studies conducted (with increasing sophistication) in the decades since the discovery of DBPs does not point to clear adverse effects on health. Findings are most consistent in relation to a risk of bladder cancer. Yet IPCS in 2000 commented that the evidence was insufficient to conclude causality and 16 years on, this remains the case. Anomalies in study findings and weaknesses in study design have also been pointed out. With diseases (such as cancer) that have a long latency between 'exposure' and development of disease, it is difficult for epidemiological studies to accurately take account of such a time lag. Thus projecting historical exposures backwards from recent levels is likely to underestimate any contribution. Studies often use THMs as a measure of exposure, yet the exposure is much too low to explain the suggested increased risks. Indeed, summing cancer risk estimates for all known DBPs would not account for that risk. If the risks are real, and result from DBPs, the responsible agents remain to be identified. Epidemiological evidence about risks of other cancers is inconsistent and inconclusive.

As regards reproductive and developmental effects, while the epidemiological evidence contains some findings suggesting associations with specific reproductive or developmental endpoints, there are similarly studies which show no such effect. The most recent review concluded that the evidence suggested only minor effects from very high doses during pregnancy on parameters such as foetal growth and birth weight. The overall evidence across these and other parameters from pre-term birth, stillbirth and congenital anomalies to semen quality is further viewed as conflicting and inconclusive.

Almost all epidemiological studies of cancer and reproductive effects relate to potable water, but as exposures to DBPs from pools and cleaning are lower, the likelihood of any risk is correspondingly lower.

The epidemiological evidence regarding respiratory illness associated with swimming pools shows positive associations in highly-exposed groups such as pool workers and professional swimmers, though reverse causation is a significant possibility in the latter case. Whilst early studies, notably among a group of schools in Belgium, suggested increased risks of asthma among child swimmers, more recent, larger prospective studies have not found any such association; indeed there is evidence suggesting improved lung function. As such, health authorities have declared that the health benefits of swimming in well-managed pools, including for asthma sufferers, outweighs any possible respiratory risks from DBPs.

The epidemiological evidence suggesting increased risks of asthma-like symptoms among professional cleaners using bleach is primarily from Spain, and relates more to professional domestic rather than institutional cleaners. Exposure to irritants in the air would be expected to be a trigger, and perhaps exacerbate symptoms in existing sufferers, but the extent to which any new condition may be created, and whether this arises from normal use, or from misuse or accidents, remains unclear.

In summary, the benefits of active chlorine in protecting against infectious disease through its widespread use to disinfect drinking water, swimming pools, surfaces and other items are clear, as are the grave consequences of neglecting such use. The World Health Organisation continues to emphasise that standards of protection of potable water must not be compromised because of concerns about possible risks from disinfection by-products. The evidence summarised in this dossier fully supports the correctness of this view and, given the generally lower exposures involved, supports a similar conclusion in relation to use to protect against infection in swimming pools and other areas.

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